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# CONTENTS OF VOLUME XVII

NUMBER 1, MAY-JUNE, 1950

	PAGE
DEFECTIVE THERMAL COAGULATION OF BLOOD IN CANCER AND OTHER DISEASES AND ITS CLINICAL INTERPRETATION. <i>George B. Jerzy Glass, M.D.</i> .....	1
URINARY EXCRETION OF STILBAMIDINE AND 2-HYDROXYSTILBAMIDINE. <i>A. Saltzman, M.D., Z. T. Tang, M.D., F. Lieben, M.D. and I. Snapper, M.D.</i> .....	21
DIHYDROERGORNINE IN THE DIFFERENTIAL DIAGNOSIS OF FUNCTIONAL HEART DISTURBANCES AND ORGANIC DISEASE. <i>Leon Pordy, M.D., Harold S. Orai, M.D. and Arthur M. Master, M.D.</i>	26
EXCLUSION OF THE DOG HEART BY PARABIOSIS. <i>Lester Blum, M.D. and Samuel J. Megibow, M.D.</i> .....	38
ANOTHER OCCUPATIONAL MARK. <i>Howard T. Behrman, M.D.</i> .....	44
A NEW APPROACH TO THE ROENTGEN THERAPY OF CANCER WITH THE USE OF A GRID. <i>Hirsch Marks, M.D.</i> .....	46
DEPTH DOSE CURVES FOR TREATMENT GRIDS IN RADIOTHERAPY. <i>Robert Loevinger, Ph.D., and Welbert Minowitz, B.E.E.</i> .....	49
LIFE'S LATER YEARS STUDIES IN THE MEDICAL HISTORY OF OLD AGE. <i>Frederick D. Zeman, M.D.</i> .....	53
ABSTRACTS.....	69
BOOK REVIEW.....	78

## NUMBER 2, JULY-AUGUST, 1950

PHYSIOLOGY OF CHOLESTEROL METABOLISM IN MAN. <i>S. J. Thannhauser, M.D., Ph.D.</i> .....	79
AN ULTRAVIOLET SPECTROPHOTOMETRIC METHOD FOR THE DETERMINATION OF $\Delta^{3,5}$ ANDROSTADIENONE-17 IN THE URINE. <i>Louis J. Soffer, M.D., Jacob Chanley, Ph.D., Mildred D. Jacobs, A.B., and H. Peter Laqueur, M.D.</i> .....	98
THE ROLE OF ANTIBODIES IN INSULIN RESISTANCE. REPORT OF A CASE. <i>Robert M. Berne, M.D. and Robert S. Wallerstein, M.D.</i> ...	102
HODGKIN'S DISEASE LOCALIZED TO THE ANTERIOR MEDIASTINUM: CLINICAL, ROENTGEN AND SURGICAL CONSIDERATIONS. <i>Emanuel Saltzman, M.D.</i> .....	112
HEMANGIOMA OF THE PONS. CASE REPORT AND REVIEW OF THE LITERATURE. <i>Philip S. Bergman, M.D.</i> .....	119
INSPIRATORY INCREASE OF THE PULSE AMPLITUDE, ITS RELATION TO PULSUS PARADOXUS, <i>Marvin C. Becker, M.D., Donald S. Kent, M.D. and Irving G. Kroop, M.D.</i> .....	132
RESTORED VIABILITY OF IMPLANTED PRESERVED NECROCARTILAGE IN RHINOPLASTY. <i>Irving Goldman, M.D.</i> .....	142
ABSTRACTS.....	145

## NUMBER 3, SEPTEMBER-OCTOBER, 1950

	PAGE
THE POOL OF MISCIBLE URIC ACID IN NORMAL AND GOUTY MAN, STUDIED WITH THE AID OF ISOTOPIC NITROGEN. <i>DeWitt Stetten, Jr., M.D.</i> .....	149
SODIUM, WATER AND EDEMA. <i>John P. Peters, M.D.</i> .....	159
THROMBOPHLEBITIS SECONDARY TO ACUTE RESPIRATORY INFECTION. <i>Robert S. Wallerstein, M.D.</i> .....	176
GALLSTONE OBSTRUCTION OF THE DUODENUM: CASE REPORT. <i>Richard M. Alexander, M.A., M.D.</i> .....	183
CASE OF COEXISTENT BENIGN AND MALIGNANT BONE TUMORS. <i>Jacob F. Katz, M.D., and Frederick M. Marek, M.D.</i> .....	187
THE MOUTH IN DIABETES MELLITUS. <i>Emanuel Knishkowsky, D.D.S., Philip Person, D.D.S., and Herbert Pollack, M.D.</i> .....	192
ABSTRACTS.....	203

## NUMBER 4, NOVEMBER-DECEMBER, 1950

HYALURONIDASE INHIBITOR OF HUMAN BLOOD SERUM IN HEALTH AND DISEASE. <i>David Gliek, Ph.D.</i> .....	207
BACTERIOLOGICAL ASPECTS OF THE PATHOGENESIS OF TUBERCULOSIS. <i>Rene J. Dubos, Ph.D.</i> .....	229
THE EFFECTS OF THE SINGLE AND DOUBLE "TWO-STEP" EXERCISE TESTS UPON THE ELECTROCARDIOGRAMS OF 200 NORMAL PERSONS. <i>Leonard Scherlis, M.D., Avery A. Sandberg, M.D., Joseph Wener, M.D., Joseph Dvorkin, M.D., and Arthur M. Master, M.D.</i> ....	242
AMYLOID DISEASE OF THE URINARY BLADDER. <i>H. E. Leiter, M.D.</i> ....	254
CARCINOID OF THE DUODENUM. <i>Charles Polivy, M.D.</i> .....	260
OBITUARY—DR. MEYER.....	265
ABSTRACTS.....	267
BOOK REVIEW.....	268

## NUMBER 5, JANUARY-FEBRUARY, 1951

	PAGE
RESEARCH ON CARDIOVASCULAR DISEASE AND CONGENITAL HEART DISEASE AT THE MOUNT SINAI HOSPITAL. <i>Saul Jarcho, M.D.</i> ...	269
THE TECHNIQUE OF CARDIAC CATHETERIZATION AND ANGIOCARDIO- GRAPHY AS EMPLOYED AT THE MOUNT SINAI HOSPITAL. <i>Marcy L. Sussman, M.D., Alvin J. Gordon, M.D., Sigmund A. Brahms, M.D., Bernard M. Schwartz, M.D., Arthur Grishman, M.D., Morris F. Steinberg, M.D., and Frederick H. King, M.D.</i> .....	272
ELECTROCARDIOGRAPHIC ABNORMALITIES INDUCED BY CARDIAC CATHETERIZATION. <i>Richard P. Lasser, M.D., Raymond Borun, M.D., Alvin J. Gordon, M.D., and Frederick H. King, M.D.</i> ....	295
FURTHER EXPERIENCES WITH MICROPLETHYSMOGRAPHY IN THE STUDY OF CONGENITAL HEART DISEASE. <i>Raymond S. Megibow, M.D., and Sergei Feitelberg, M.D.</i> .....	303

AORTIC SEPTAL DEFECT SIMULATING PATENT DUCTUS ARTERIOSUS. <i>Frederick H. King, M.D., Alvin J. Gordon, M.D., Sigmund Brahms, M.D., Richard Lasser, M.D., and Raymond Borun, M.D.</i>	310
ISOLATED INTERVENTRICULAR SEPTAL DEFECT WITH DILATATION OF THE PULMONARY ARTERY, AN ENTITY. <i>Irving G. Kroop, M.D., Raymond Borun, M.D., Richard P. Lasser, M.D., Alvin J. Gordon, M.D., Sigmund A. Brahms, M.D., and Frederick H. King, M.D.</i>	317
UNCOMPLICATED PULMONARY STENOSIS. <i>Bernard M. Schwartz, M.D., Alvin J. Gordon, M.D., Sigmund A. Brahms, M.D., and Frederick H. King, M.D.</i>	323
TRICUSPID ATRESIA WITH TRANSPOSITION OF THE GREAT VESSELS: SUCCESSFULLY TREATED BY SURGERY. <i>Sidney Blumenthal, M.D., Sigmund Brahms, M.D., and Marcy L. Sussman, M.D.</i>	328
ABERRANT INSERTION OF PULMONIC VEINS. <i>Arthur Grishman, M.D., Sigmund A. Brahms, M.D., Alvin J. Gordon, M.D., and Frederick H. King, M.D.</i>	336
ABSTRACTS	344

## NUMBER 6, MARCH-APRIL, 1951

	PAGE
DR. ALBERT A. BERG. A MEMOIR. <i>Ernest E. Arnsheim, M.D.</i>	351
SCIENTIFIC RESEARCH IN MODERN HOSPITAL PRACTICE. <i>George Bachr, M.D.</i>	353
SOME OF THE PRINCIPLES AND METHODS CONTRIBUTED BY THE SERV- ICE OF DR. A. A. BERG. <i>Leon Ginzburg, M.D.</i>	356
TOWERING MEN OF MEDICINE. <i>Bertram M. Bernheim, M.D.</i>	369
DR. A. A. BERG: AN APPRECIATION. <i>Leopold Stieglitz, M.D.</i>	370
CONSENT FOR OPERATION. <i>Joseph Turner, M.D.</i>	373
SURGICAL TREATMENT IN ACUTE HEMORRHAGE OF PEPTIC ULCERS. <i>H. Finsterer, M.D.</i>	377
THE ROMANCE OF THE MODERN ERA OF BLOOD TRANSFUSION. <i>Richard Lewisohn, M.D.</i>	393
VAGOTOMY IN THE TREATMENT OF PEPTIC ULCER NEAR THE CARDIA AND OF PEPTIC ULCER OF JEJUNUM (MARGINAL ULCER, STOMAL- ULCER). <i>Felix Mandl, M.D.</i>	409
VAGOTOMY AND SUBTOTAL GASTRIC RESECTION WITH VAGOTOMY IN CASES OF GASTROJEJUNAL AND GASTROJEJUNOCOLIC ULCERS AND FISTULAS AFTER MULTIPLE PREVIOUS SURGICAL PROCEDURES. <i>Wallman Walters, M.D., and James R. Hoon, M.D.</i>	423
OBSERVATIONS ON GASTRECTOMY FOR CHRONIC DUODENAL ULCER WITH PARTICULAR REFERENCE TO GASTRECTOMY WITH AND WITH- OUT INFRADIAPHRAGMATIC VAGOTOMY. <i>Percy Klingenstein, M.D., Ralph Colp, M.D., Leonard J. Druckerman, M.D., and Vernon A. Weinstein, M.D.</i>	429
PRESERVATION OF THE PYLORIC ANTRUM IN RESECTION OF HIGH GASTRIC LESIONS. <i>Rudolph Nissen, M.D.</i>	442
PUDENDAL HERNIA. REPORT OF A CASE OPERATED UPON BY THE AB- DOMINAL ROUTE. <i>John H. Garlock, M.D., and Alvin A. Bakst, M.D.</i>	450
THE RESULTS OF SPHINCTEROTOMY IN PANCREATITIS. <i>Henry Doubilet, M.D., and John M. Mulholland, M.D.</i>	458



AVULSION OF THE DIAPHRAGM. <i>Moses Behrend, M.D., Albert Behrend, M.D., and Gladys Rosenstein, M.D.</i> .....	463
CARCINOMA OF THE GALL BLADDER. A REPORT OF 32 CASES. <i>Max Danzis, M.D.</i> .....	467
EPIDERMOID CARCINOMA OF THE ANAL CANAL. <i>H. E. Bacon, M.D., R. Ventura, M.D., and I. Sauer, M.D.</i> .....	478
THE PRESENT STATUS OF THE SURGICAL TREATMENT OF CANCER OF THE COLON AND RECTUM. <i>Samuel H. Klein, M.D.</i> .....	486
DIRECT ARTERIOVENOUS ANASTOMOSIS. <i>W. Wayne Babcock, M.D.</i> ...	499
METHOD FOR THE TERMINO-VEINOS AND VENO-ARTERIOUS ANASTOMOSES. <i>R. Paolucci, M.D., and E. Tosatti, M.D.</i> .....	506
PERIPHERAL ARTERIAL EMBOLISM. <i>Samuel Silbert, M.D.</i> .....	517
RETROPERITONEAL SARCOMA (ADRENAL TUMOR?) WITH ACTIVE HEMORRHAGE. A SURGICAL EMERGENCY RESECTION. TWENTY-SEVEN YEAR FOLLOW-UP. <i>Harold Neuhoof, M.D.</i> .....	520
PRIMARY IDIOPATHIC SEGMENTAL HEMORRHAGIC INFARCTION OF THE GREATER OMENTUM. <i>Gabriel P. Seley, M.D.</i> .....	523
RETRO-CECAL ABSCESS, A LATE SEQUELA OF ACUTE GANGRENOUS APPENDICITIS. <i>Thomas J. Sullivan, M.D.</i> .....	526
SURGERY OF THE NEWBORN. <i>Ernest E. Arnheim, M.D.</i> .....	528
CONGENITAL ATRESIA OF THE BILE DUCTS. <i>Alfred A. Strauss, M.D.</i> ...	552
ACUTE APPENDICITIS WITH MALROTATION OF THE CAECUM. CASE REPORT. <i>Gertrude Felslin, M.D.</i> .....	563
TECHNICAL PRINCIPLES IN MYOMECTOMY WITH SPECIAL REFERENCE TO HEMOSTASIS. <i>I. C. Rubin, M.D.</i> .....	565
PROLAPSE OF THE UTERUS. A REVIEW OF 722 CASES TREATED BY THE PARAMETRIAL FIXATION OPERATION. <i>Morris A. Goldberger, M.D., and David Zakin, M.D.</i> .....	571
FIBRO-ADENOMA OF THE OVARY WITH ASCITES AND HYDROTHORAX (MEIGS' SYNDROME). <i>Abraham E. Jaffin, M.D.</i> .....	596
TORSION OF THE FALLOPIAN TUBE PRODUCING GANGRENE OF THE SMALL INTESTINE. <i>Louis Burke, M.D., Arthur N. Davids, M.D., and Gabriel Seley, M.D.</i> .....	605
CESARIAN SECTION AFTER COLECTOMY FOR ULCERATIVE COLITIS. <i>Emanuel Klempner, M.D.</i> .....	610
ENDOMETRIOSIS IN A LAPAROTOMY SCAR. REPORT OF A CASE WITH UTERO-ABDOMINAL FISTULA. <i>Nathan Mintz, M.D., and Joseph A. Gains, M.D.</i> .....	613
RECURRENT CERVICAL METASTATIC CANCER. TWO CASE REPORTS. <i>Harry C. Saltzstein, M.D.</i> .....	618
INTESTINAL OBSTRUCTION COMPLICATED BY PREGNANCY. <i>Robert I. Walter, M.D.</i> .....	625
CALCULOSIS OF THE URINARY TRACT IN EGYPT. <i>J. Bitschai, M.D.</i> ....	630
RENAL PTOSIS. <i>Elmer Hess, M.D., Russell B. Roth, M.D., and Anthony F. Kaminsky, M.D.</i> .....	644
SUPRAPUBIC PROSTATECTOMY WITH HEMOSTASIS BY TRANSURETHRAL FULGURATION AND PRIMARY CLOSURE OF THE BLADDER. <i>Abraham Hyman, M.D., H. E. Leiter, M.D., and Stanley I. Glickman, M.D.</i> .....	652
LIPOMYOSARCOMA OF THE KIDNEY: REPORT OF TWO CASES. <i>Leo Edelman, M.D.</i> .....	659
PAPILLARY CARCINOMA OF THE URETER AND BLADDER THIRTEEN YEARS POST-NEPHRECTOMY FOR PAPILLARY CARCINOMA OF THE KIDNEY. <i>Gordon D. Oppenheimer, M.D., and Harold Lear, M.D.</i> ...	671

CONGENITAL ECTOPIC HYDRONEPHROTIC KIDNEY SIMULATING AN IN- TRAPERITONEAL LESION. <i>M. Swick, M.D.</i> .....	675
PULMONARY DECORTICATION IN CIVILIAN PRACTICE. <i>Arthur S. W.</i> <i>Touroff, M.D., and Gabriel Seley, M.D.</i> .....	680
PNEUMONECTOMY FOR PRIMARY LOCALIZED LYMPHOMA. <i>Arthur H.</i> <i>Aufses, M.D.</i> .....	693
EXTRAPLEURAL PULMONARY RESECTION (PLEUROPNEUMONECTOMY). <i>Irving Arthur Sarot, M.D.</i> .....	700
THE MIDDLE LOBE SYNDROME. <i>Isidor Kross, M.D., and Milton B.</i> <i>Rosenblatt, M.D.</i> .....	711
NOTES ON SUBPIRENIC ABSCESS. <i>Coleman B. Rabin, M.D.</i> .....	717
BILATERAL TRIGEMINAL NEURALGIA. <i>Roland M. Klemme, M.D.</i> .....	729
TUMORS OF THE INTRACRANIAL PORTION OF THE OPTIC NERVE. <i>Ira</i> <i>Cohen, M.D.</i> .....	738
SPONTANEOUS OCCLUSION OF THE INTERNAL CAROTID ARTERY IN THE NECK. <i>Sidney W. Gross, M.D.</i> .....	746
AN IMPROVED OSTEOPLASTIC EXPOSURE OF THE TEMPORO-OCCIPITAL REGION. <i>Benno Schlesinger, M.D.</i> .....	750
DEPRESSED FRACTURE OF THE TIBIAL PLATEAU. A SIMPLE SURGI- CAL METHOD FOR ELEVATION AND FIXATION OF THE DEPRESSED FRAGMENT. <i>Robert K. Lippmann, M.D.</i> .....	761
LIPOMA PETRIFICUM OSSIFICANS OR LIPOMA WITH HETEROTOPIC OSSI- FICATION. <i>Albert J. Schein, M.D.</i> .....	769
HYPERPARATHYROIDISM. <i>I. Snapper, M.D., and D. Rosenthal, M.D.</i> ...	774
BLOOD IODINE AND I-131 EXCRETION IN DIAGNOSTIC PROBLEMS OF HYPERTHYROIDISM. <i>Solomon Silver, M.D., Stephen B. Yohalem,</i> <i>M.D., and Mack H. Fieber, M.D.</i> .....	781
THE SIMULTANEOUS OCCURRENCE OF ACTIVE PEPTIC ULCER AND ACTIVE HYPERTHYROIDISM. <i>A. L. Garbat, M.D.</i> .....	787
CHANGING PATTERNS IN THE DEFINITION OF ACUTE LUPUS ERY- THEMATOSUS. <i>Paul Klemperer, M.D.</i> .....	793
SARCOIDOSIS IN RELATION TO TUBERCULOSIS. <i>Eli Moschowitz,</i> <i>M.D.</i> .....	799
PEPTIC ULCER—PRESENT DAY MEDICAL THERAPIES. <i>Asher Winkel-</i> <i>stein, M.D.</i> .....	808
MULTIPLE EROSIONS AND ACUTE PERFORATIONS OF THE ESOPHAGUS, STOMACH, AND DUODENUM IN RELATION TO DISORDERS OF THE NERVOUS SYSTEM. <i>Joseph H. Globus, M.D., and Bruce L. Ralston,</i> <i>M.D.</i> .....	817
GASTROENTEROLOGY AS A SURGICAL SPECIALTY AT THE MOUNT SINAI HOSPITAL. <i>Burrill B. Crohn, M.D.</i> .....	843
SURGICAL ASPECTS OF PEPTIC ULCER. <i>Sidney Grossman, M.D.</i> .....	848
CHANGES IN GASTRIC ACIDITY AND MOTILITY IN A CASE OF BILATERAL SUBPHRENIC VAGOTOMY ALONE FOR DUODENAL ULCER (11 YEAR FOLLOW-UP OF IMMEDIATE AND LATE RESULTS). <i>Albert Cornell,</i> <i>M.D.</i> .....	855
THE GASTRIC POUCH FROM ITS ORIGINS TO THE PRESENT (AN HISTOR- ICAL STUDY IN THE METHODOLOGY OF GASTRIC PHYSIOLOGICAL RESEARCH, WITH PARTICULAR REFERENCE TO THE CONTRIBU- TIONS OF PAVLOV). <i>Franklin Hollander, Ph.D.</i> .....	872
MALROTATION OF THE INTESTINE. <i>Leo H. Pollock, M.D.</i> .....	886
MELANOMA OF THE SMALL INTESTINE AND STOMACH. <i>Alexander Rich-</i> <i>man, M.D., and Joan J. Lipsay, M.D.</i> .....	907

MUCOSAL AEROGRAPHIC STUDIES OF THE STOMACH AND SMALL BOWEL. <i>Arthur J. Bendick, M.D.</i> .....	917
THE RELATION OF NEUROCIRCULATORY ASTHENIA TO ANXIETY NEUROSIS. <i>B. S. Oppenheimer, M.D., and Menard M. Gertler, M.D.</i> ...	924
THE PSYCHOSOMATIC APPROACH TO NEUROCIRCULATORY ASTHENIA— A SUPPLEMENT TO "THE RELATION OF NEUROCIRCULATORY AS- THENIA TO ANXIETY NEUROSIS." <i>Sidney G. Margolin, M.D.</i> .....	930
THE CARDIAC PATIENT AND OPERATION. <i>Arthur M. Master, M.D., and Harry L. Jaffe, M.D.</i> .....	934
PSYCHODYNAMIC FACTORS IN SURGERY. <i>Solon S. Bernstein, M.D., and S. Mouchly Small, M.D.</i> .....	938
FETAL DEFECTS RESULTING FROM VIRAL DISEASE OF THE PREGNANT MOTHER. <i>Murray H. Bass, M.D.</i> .....	959
OBSERVATIONS ON BLOOD PRESSURE IN CHILDREN FOLLOWING AN ACUTE GLOMERULO-NEPHRITIS. <i>Sam de Lange, M.D., and Jerome L. Kohn, M.D.</i> .....	971
OBSERVATIONS ON THE USE OF DIGITALIS IN THE TREATMENT OF CHRONIC CONSTIPATION AND ALLIED CONDITIONS. <i>Albert A. Ep- stein, M.D.</i> .....	980
THE RICE DIET IN THE TREATMENT OF THE AMBULATORY HYPERTEN- SIVE PATIENT. <i>David Adlersberg, M.D., Leon Bader, M.D., and Harold B. Trachtenberg, M.D.</i> .....	990
A SIMPLE TEST FOR EXTENT OF SYMPATHECTOMY. <i>Henry D. Janowitz, M.D., and M. I. Grossman, M.D.</i> .....	1004
THE ROLE OF ACCESSORY SPLEENS IN POST-SPLENECTOMY RECURRENT PURPURA HEMORRHAGICA. <i>N. Rosenthal, M.D., P. Vogel, M.D., S. Lee, M.D., and Joan J. Lipsay, M.D.</i> .....	1008
A SURVEY OF SOME RECENTLY PROPOSED CHEMICAL TESTS FOR MALIG- NANCY. <i>Harry Sobotka, Ph.D.</i> .....	1021
THE USE OF RADIOACTIVE AND STABLE ISOTOPES IN HEMATOLOGY. <i>L. R. Wasserman, M.D., I. A. Rashoff, M.D., and T. F. Yoh, M.D.</i> .....	1037
X-RAY DIFFRACTION ANALYSIS OF MIXTURES CONTAINING SODIUM SALTS OF FATTY ACIDS. <i>Gerda Gershein Mayer, Ph.D., Herman S. Kaufman, Ph.D., and S. M. Peck, M.D.</i> .....	1048
ABDUCENS NERVE PALSY FOLLOWING SPINAL ANESTHESIA. <i>Milton H. Adelman, M.D., and Sidney S. Lyons, M.D.</i> .....	1055
BALLISTOCARDIOGRAPHY—A REVIEW. <i>Louis B. Turner, M.D.</i> .....	1060
THE CLINICAL PICTURE OF CEREBRAL ARTERIOSCLEROSIS WITH PAR- TICULAR REFERENCE TO THE AGED. <i>Frederick D. Zeman, M.D.</i> ...	1075
THE TREATMENT OF NEUROBLASTOMA. <i>Sidney M. Silverstone, M.D., and William Harris, M.D.</i> .....	1083
THE TREATMENT OF PTERYGIUM BY SIMPLE EXCISION. <i>David Wexler, M.D.</i> .....	1092
CLOSURE OF PHARYNGOSTOME BY DISTANT OPEN LINED FLAP. <i>Joseph L. Goldman, M.D., and Samuel M. Bloom, M.D.</i> .....	1096
SURGERY FOR DEAFNESS IN CONGENITAL ATRESIA OF THE EXTERNAL AUDITORY CANAL (WITH REPORT OF A CASE). <i>Samuel Rosen, M.D.</i> ...	1104
WHAT IS JUSTIFIABLE SURGICALLY IN MÉNIÈRE'S DISEASE? <i>Harry Rosenwasser, M.D.</i> .....	
RECONSTRUCTION OF THE LARYNX AND THE TRACHEA. REPORT OF A CASE OF EXTENSIVE CICATRICIAL STENOSIS. <i>Max L. Som, M.D.</i> ...	1109
ABSTRACTS .....	1127
INDEX .....	1133



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## CONTENTS

	PAGE
DEFECTIVE THERMAL COAGULATION OF BLOOD IN CANCER AND OTHER DISEASES AND ITS CLINICAL INTERPRETATION. <i>George B. Jerzy Glass, M.D.</i> .....	1
URINARY EXCRETION OF STILBAMIDINE AND 2-HYDROXYSTILBAMIDINE. <i>A. Saltzman, M.D., Z. T. Tang, M.D., F. Lieben, M.D. and I. Snapper, M.D.</i> .....	21
DIHYDROERGORNINE IN THE DIFFERENTIAL DIAGNOSIS OF FUNCTIONAL HEART DISTURBANCES AND ORGANIC HEART DISEASE. <i>Leon Pordy, M.D., Harold S. Orai, M.D. and Arthur M. Master, M.D.</i> .....	26
EXCLUSION OF THE DOG HEART BY PARABIOSIS. <i>Lester Blum, M.D. and Samuel J. Megibow, M.D.</i> .....	38
ANOTHER OCCUPATIONAL MARK. <i>Howard T. Behrman, M.D.</i> .....	44
A NEW APPROACH TO THE ROENTGEN THERAPY OF CANCER WITH THE USE OF A GRID. <i>Hirsch Marks, M.D.</i> .....	46
DEPTH DOSE CURVES FOR TREATMENT GRIDS IN RADIOTHERAPY. <i>Robert Loevinger, Ph.D., and Welbert Minowitz, B.E.E.</i> .....	49
LIFE'S LATER YEARS STUDIES IN THE MEDICAL HISTORY OF OLD AGE. <i>Frederick D. Zeman, M.D.</i> .....	53
ABSTRACTS.....	69
BOOK REVIEW.....	78

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IN CANCER AND OTHER DISEASES AND ITS  
CLINICAL INTERPRETATION<sup>1</sup>

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## INTRODUCTION

The growing interest in defective thermal coagulation of serum is in part the result of recently developed tests based upon this phenomenon which are recommended for detection of cancer. It seems timely therefore to discuss the principles upon which these tests are based, and the methods for determination of defective thermal coagulation of serum. It will perhaps also be of interest to mention some historical data pertaining to this phenomenon. Two questions need first to be answered, namely 1) whether the principle of defective thermal coagulation of blood serum can be used for cancer diagnosis because of its intrinsic merits, and 2) what place does thermal coagulation of the serum hold among other clinical serological reactions, not only with respect to cancer but also in other pathological conditions and clinical problems.

First of all it must be recognized that thermal coagulation of blood serum has nothing in common with the process of blood coagulation, since no substance which takes part in blood clotting plays a part in thermal coagulation of blood serum. The process of thermal coagulation of blood serum should also not be identified with the heat coagulation of serum proteins, because under the latter name is understood most frequently the precipitation of serum proteins which occurs if the diluted serum is heated in the presence of electrolytes. This heat coagulation of serum proteins is closely related to the precipitation of serum proteins under the influence of precipitating or dehydrating agents, to the immunological agglutination reactions, and to the non-specific serological flocculation tests, like Weltmann heat coagulation band, Takata Ara reaction or Hanger cephalin-cholesterol flocculation test. In all these processes the flocculation of serum proteins is due to the aggregation of protein molecules or *micelles* and the main role in this process is attributed to the flocculation of globulins, and especially of the *gamma*-globulin fraction (1, 2).

The coagulation of the blood serum is a quite different physico-chemical process. If any of the following reagents: concentrated formol, diluted lactic or propionic acid, or alcohol, is added to the serum in appropriate concentrations the viscosity of the latter rapidly increases, and shortly or in a few hours the jelly-like structure of serum gel forms. This phenomenon is the basis of several serological gelification reactions (3-5). Similar changes occur, if the normal un-

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diluted serum is heated above its critical temperature, i.e. 56°C. (6). First of all, there is an increase in viscosity and turbidity of the heated serum, which still remains liquid (heat turbidity stage). If the heating is continued the viscosity increases still further and a loose jelly-like structure forms, which exhibits thixotropy (heat gelification stage). If the heating is continued beyond this stage, a further change in the state of dispersion occurs, characterised by formation of the clot, i.e. a solid coagulum of the serum, which has almost the same volume as previously taken by the fluid (heat coagulation stage).

Until recently the mechanism of heat coagulation of the serum was universally attributed to the heat aggregation of the protein molecules. Since, however, the same process of aggregation is responsible for flocculation reactions it was not clear why the same process of aggregation in one instance causes flocculation, while in the other—gelification or coagulation of serum *en bloc*.

Only the recent studies of Lecomte du Noy (6) have revealed fundamental differences between the heat flocculation or precipitation and the thermal coagulation of blood serum. Extensive physico-chemical studies based upon measurement of viscosity, rotatory power and dispersion, absorption and scattering of light, and polarization phenomena yielded almost conclusive evidence that the thermal coagulation and gelification of blood serum do not depend upon the aggregation but upon the intramolecular hydration of protein molecules. During heating the increased kinetic energy of water particles which form the solvent of protein molecules causes the penetration of water into the intramolecular space and its adsorption between the ramified chains of complex structure of proteins. This results in gradual increase of the volume of each molecule. The more water enters the protein molecules and the less water remains as a solvent the more viscous the serum turns and the more it approaches the gel-like structure. When finally the whole volume of water becomes incorporated intramolecularly, and no water is present as a solvent—a state which should increase the linear dimensions of protein molecules about two times and volume about 9 times—the gel solidifies into a solid clot (coagulum).

If normal undiluted serum is heated, the formation of serum gel or coagulum would depend upon the amount of heat, which is applied to the serum. This is the function of the increase in temperature and the duration of heating, if all other factors remain unchanged (the mass and the specific heat). From this it is evident that the thermal coagulation process may be measured by varying either factor, i.e. time and temperature, or more easily, by varying the temperature alone and keeping the time constant. The effect of heating upon the serum may be determined in both instances by measuring the turbidity or viscosity changes during heating, or more easily by determining the temperature at which either gelification of the serum or its complete coagulation occurs. In the past, thermal coagulation tests in serum were as a rule done by one of these methods. The minimal temperature necessary for formation of a serum gel or coagulum is called the thermal gelification point or the thermal coagulation point of blood serum respectively. Prolongation of the heating time lowers these points, but only to a critical level, below which the state of dispersion of the serum no longer undergoes any change.

## A FEW HISTORICAL DATA

The first studies on thermal coagulation of blood serum done in 1894 are credited to Halliburton (7). He was followed in 1906 by Mellanby (8). They found that various protein fractions present in normal and pathological sera showed different thermal gelification points, the range of which was between 56 and 100°C. Schade in 1909, using a turbidity method (9), found differences in various pathological sera on heating. In the years between 1918 and 1927, several European investigators studied the thermal gelification of blood serum in a limited number of cases. The following names should be mentioned in this connection: Belak (10), Koopman (11), Mayer (12), Rosenow (13), Hachez (14), Cossu (15), Ehrentheil and Weiss-Ostborn (16), Mayr and Hofstadt (17) and Muller (18). All their studies were conducted with methods in which the turbidity or gelification stage was determined. These methods revealed rather small and insignificant deviations in pathologic states. The neoplastic diseases were not included in these studies in appreciable numbers, so that no inferences concerning general significance of thermal coagulation defect for cancer diagnosis were made.

While studying qualitative disturbances in serum proteins, I developed in 1936 a new technic for the study of thermal coagulation. This method yielded a wider range of variations in the thermal coagulation point of serum under pathological conditions (19). In this technic the final coagulation stage instead of the initial turbidity or gelification as the end point of the reaction was utilised. The thermal coagulation point of serum (TCPS)<sup>2</sup> was determined as the minimal temperature which, if applied for 1 minute, suffices to coagulate the serum to such extent that the clot formed no longer exhibits thixotropy and does not break when subject to standardized powerful shaking for 10 seconds. The cohesion of the gel shattered was ascertained by addition of the hypertonic salt solution to observe the flotation of the broken gel.

With this technic it was found that normally serum coagulated between 75 and 80°C., but that in many instances under pathological conditions the TCPS was increased to a considerable extent (19). This increase was arbitrarily classified as 1 plus, if the serum coagulated between 81° and 83°, 2 plus—if between 84° and 89°, 3 plus—if between 90° and 95°, and 4 plus—if the serum did not coagulate even at 95°C. In this instance the serum usually did not coagulate also at the temperature of 100°C., but sometimes it could be coagulated below the boiling point of serum at the range of 105°–110°C.

Four hundred samples of sera were tested by this method (19) of which 103 were obtained from cancer patients. It was found that sera of patients suffering from cancer and particularly those with a neoplasm involving the abdominal viscera, showed an increased TCPS 2, 3 or 4 plus, i.e. 84°C. or above. While this change in TCPS was very obvious in patients with cancer and occurred in 63.2 per cent of neoplasms of abdominal organs, it was found also in late pregnancy, nephrosis, cardiac failure, severe infections, active pulmonary tuberculosis, pneumonia, pyogenic processes etc. Consequently, it was concluded that the defective thermal coagulation was not specific for cancer, but that its determination was helpful in the diagnosis of some selected groups of malignancies, especially in cancer of abdominal organs. This paper was published in French 14 years ago under the title: "The significance of the determination of the thermal coagulation point of blood serum for the clinical evaluation of various diseases and for the diagnosis of some malignant neoplasms" (19). It was the first paper to formulate the principle of defective thermal coagulation of blood serum in cancer and the non-specificity of this principle.

Since that time the number of sera studied by this method has increased considerably, so that at present a series of 1500 tests of TCPS is available (20), which were performed in about 160 cancer cases and 1000 controls, collected from normals and various non-neoplastic diseases.

Twelve years after the publication of the first paper (19) on thermal coagulation in can-

<sup>2</sup> Form here on the letters "TCPS" will be used to indicate the "Thermal Coagulation Point of Serum."



cer, two groups of investigators returned to the thermal coagulation process as means to cancer diagnosis, apparently unaware of their predecessors in this field.

Black, Kleiner and Bolker in 1948 suggested the testing of the thermal coagulation of plasma for the diagnosis of malignancy (21), and recommended it as an auxiliary test to their methylene blue "blood test for cancer" (22-24). In spite of its name it is a heat turbidity reaction rather than a real coagulation test. Since it is run in plasma and depends therefore upon the disturbances also in the fibrinogen content, the results of this test cannot be compared with other thermal coagulation tests run in serum, and, in order to avoid confusion, this test will not be discussed within the frame of this paper.

Huggins, Miller and Jensen in 1949 published a new technic for the determination of the thermal coagulation of serum (25, 26) which was based upon their earlier studies dealing with chemical substances preventing or promoting this process (27). Since these investigations revealed that halogenated acetates and especially a solution of iodoacetate prevents the process of thermal coagulation when added even in minimal concentration to the serum, Huggins et al. utilized this finding to determine the defect in thermal coagulation. As an indicator of the ability of the serum tested to coagulate they determined the smallest concentration of iodoacetate sufficient to prevent the gelification of serum on heating, if raised to the temperature of 100°C. for half an hour. To refine this test and make it less dependent upon content of serum proteins they calculated the so-called iodoacetate index, dividing the micromolarity of the iodoacetate used by the total protein content of serum. Based on studies of 300 patients, including about 100 with neoplasms, Huggins et al. rediscovered the principle of defective thermal coagulation of blood serum as an aid in the diagnosis of cancer and recommended it for screening early cancer cases. This was done in spite of the fact that Huggins also noted the non-specificity of the principle of defective thermal coagulation for cancer, having encountered positive tests, i.e. iodoacetate index below 9.0, in active pulmonary tuberculosis and massive infections. Because of the prominence of the author in cancer research and in view of the unequivocal presentation of this test at the meeting of the American Society for Cancer Research as "a simple though rough test for cancer" (26), this test received a vast publicity in the lay press and was introduced in some clinics and laboratories throughout the land for the purpose of general cancer diagnosis.

#### THE EVALUATION OF THE DEFECT OF THERMAL COAGULATION OF SERUM IN CANCER AND OTHER DISEASES

The principle involved in Huggins test is the same as that in the thermal coagulation defect determined with other previously mentioned technics. It might be of interest in this connection to discuss first the results which were obtained in the attempts of cancer diagnosis by the determination of thermal coagulation of blood serum with my technic in a much larger series of cases (20). The data are summarized in Table 1. Only a 2-4 plus increase in TCPS (84°C. or above) was considered as a defect in thermal coagulation, because 1 plus increase (81°-83°) was obtained in so many minor illnesses that it was regarded as nearly borderline. The diagnoses in all cases were reached by all clinical and laboratory means and verified in all cases of cancer by biopsy, operation or post mortem examination. All cases of cancer were studied before the surgical removal of the tumor.

It is evident from Table 1 that the total incidence of defective thermal coagulation in cancer was 52.5 per cent, but that the greatest deviations in TCPS were found in neoplasms of the abdominal organs (70.6 per cent) and in tumors of bones, the thyroid and the prostate (63.3 per cent). The incidence of defective thermal coagulation in cancers of other organs was much smaller and the in-

TABLE I

*Defective thermal coagulation of blood serum in various neoplastic and non-neoplastic diseases*

DIAGNOSIS	NUMBER OF CASES	INCREASED 2, 3 OR 4 PLUS THERMAL COAGULATION POINT (84°C. AND ABOVE)	
		Number of cases	Percentage
I. Normals.. (total)	60	0	0
II. Malignant tumors.. (total)	162	85	52.5
abdominal viscera	85	60	70.6
bones, thyroid, prostate	19	12	63.1
breast	11	3	27.3
skin, lip, tongue	14	3	21.4
lung	8	2	25.0
cervix, uterus	25	5	20.0
III. Normal, mainly late, pregnancy.. (total)	44	19	43.2
IV. Non-neoplastic diseases.. (total)	894	292	32.6
a. frequently associated with disturbed thermal coagulation.. (total)	407	247	60.7
Complicated pregnancy	14	14	100.0
Nephrosis, eclampsia	20	20	100.0
Extensive burns, frostbite	7	7	100.0
Ulcerative colitis, pyloric stenosis, obstructive jaundice	23	21	91.3
Bacterial endocarditis, typhoid	13	10	77.0
Pyogenic infections of abdominal and chest organs and extremities	68	50	73.5
Acute malaria	33	22	66.7
Congestive heart failure	69	45	65.2
Hodgkin's disease	13	8	61.5
Pneumonia	32	18	56.5
Pulmonary tuberculosis	79	23	29.1
Acute and subacute arthritis	36	9	25.0
b. unfrequently associated with disturbed thermal coagulation:			
Inflammatory/non-pyogenic/diseases: pleurisy, adnexitis, glomerulo-nephritis, lymphadenitis, cholecystitis, infectious hepatitis, gastritis, colitis, bronchitis. Uncomplicated diabetes mellitus. Peptic ulcer without malnutrition. Anemias of various type. Emphysema. Bronchial asthma and other allergic conditions. Uterine fibroids. Fractures. Functional disturbances of the stomach and colon. Other miscellaneous conditions.. (total)	487	45	9.3
Total	1160	396	34.1



creased TCPS was noted only in 13 out of 58 cases of cancer of the female genital organs, breasts, lips, tongue and lungs, i.e. in 22.4 per cent.

The incidence of normal TCPS in cancer (false negative test) is on the average, very large (47.4 per cent), thus precluding the use of defective thermal coagulation test as an indicator of early cancer. The percentage of false negative tests can be decreased to about 30 per cent, by including small deviations (1 plus increase) in TCPS and considering them pathological. This, however, would greatly increase the percentage of false positive tests and reduce its diagnostic significance even more.

It is also evident from the Table 1 that the defective thermal coagulation of serum is not specific for cancer and that the increased TCPS is found in many non-neoplastic forms of disease. It occurs in late pregnancy, in 43.2 per cent of cases. Moreover, it is found in a great percentage of control cases of various non-neoplastic disease. If the control cases are selected among those conditions which are known to be rather infrequently associated with disturbances in serum proteins, the percentage of false positive tests (i.e. defective thermal coagulation in non-malignant disease) will be very small and would only amount to 10.3 per cent. This percentage of false positive tests is similar to figure given by Black et al. (24) and Huggins et al. (25) for their tests. The diseases which belong to this group are listed in the Table 1. If, however, the control cases are selected from diseases which are known to be frequently associated with disturbances and depletion of serum proteins—the percentage of false positive tests in non-neoplastic diseases will be very great, as evidenced by data listed in Table 1, and would amount in this series of patients with extremely severe disease to 64.2 per cent.

This may explain why some "cancer tests" compare so favorably with controls when the latter are selected at random from among patients without any severe disease, and are not sought among those non-neoplastic conditions which are prone to provoke disturbances in proteins as do malignant tumors. A true evaluation of the diagnostic significance of the "cancer test" is possible only when the control cases are selected not at random among dispensary patients but mainly from those with severe disease on the wards of the general hospital.

It will be noted that among these diseases, pregnancy with complications (hemorrhage, infected or incomplete abortion, puerperal sepsis, premature separation of placenta, placenta previa etc.) gives 100 per cent of positive tests (increase 2-4 plus in TCPS). Nephrosis, eclampsia, extensive burns and frostbite also showed 100 per cent defective coagulation. The TCPS was also most frequently increased in severe ulcerative colitis, pyloric stenosis, obstructive jaundice of long duration, bacterial endocarditis, typhoid, acute rheumatic fever, pyogenic diseases of the chest, abdomen and extremities (abscess of the lung, empyema, cellulitis, purulent peritonitis, periappendiceal abscess, pyosalpinx, purulent parametritis etc.) as well as in many cases of malaria, and pneumonia in the febrile stage. The same holds true in severe cases of Hodgkin's disease and in advanced leukemia. The TCPS was also increased in congestive heart failure and in pulmonary tuberculosis, but only in advanced stages.

The high incidence of abnormal coagulation in non-neoplastic diseases in our

selected control cases, as well as the great percentage of false negative tests in cancers of the genital organs, skin, lips and tongue—indicates that the principle of the defective thermal coagulation can not be used for general cancer diagnosis.

Huggins et al. introduced two basically new features into the technic of determination of the thermal coagulation defect of serum, namely: 1) the measurement of the ability of the serum to coagulate, not by amount of heat required, but by the quantities of the anticoagulant (iodoacetate) needed to prevent the coagulation of serum when acted upon by the same amount of heat; 2) calculation of the coagulation defect per unit of total protein content of serum.

Do these two features introduced by Huggins et al. (25) add substantially to the value of the principle of defective thermal coagulation of serum for the diagnosis of cancer? To answer this question, I have in cooperation with Dr. Boyd and Dr. Dworecki carried out simultaneously the Huggins iodoacetate index

TABLE 2

*Correlation of thermal coagulation point with iodoacetate index in 218 pathological sera*

THERMAL COAGULATION POINT OF BLOOD SERUM	NUMBER OF CASES STUDIED IN THE GROUP	AVERAGE MICROMOLARITY OF IODOACETATE SOLUTION SUFFICIENT TO PREVENT THERMAL COAGULATION OF SERUM
°C.		
75-81	135	36.5
82-84	50	32.0
85-89	12	29.7
90-95	10	21.6
over 95	11	19.9

and the TCPS in a large series of patients with cancer of internal organs and those with non-neoplastic disease selected from among such illnesses which often show defective thermal coagulation (28).

The data listed in the Table 2 show that it is immaterial in principle whether the defect in thermal coagulation of blood serum is measured by amount of heat necessary to coagulate the serum, or by the amount of anticoagulant (iodoacetate) required to prevent its coagulation. The data on this subject obtained in 218 different pathological sera and listed in Table 2 show that there is an inverse relationship between TCPS and the concentration of iodoacetate sufficient to prevent thermal coagulation process. Although there may be some individual differences in the results of both tests (28) the correlation of both technics, especially in cases of definitely defective thermal coagulation, is in the average good. Both technics detect the same defect in thermal coagulation of serum only in a different way. The fundamental principle remains the same.

The second new feature of the Huggins technic also does not alter the non-applicability of the principle of defective thermal coagulation for the general cancer diagnosis. If the principle used in Huggins test was correct, namely that the cancer sera showed a greater defect in coagulation per unit of protein contained in serum than the non-neoplastic diseases, this should be also evidenced

by the higher average content of total serum proteins in cancer than in non-neoplastic diseases for the same TCPS. The data published previously (20), show that this is not the case. Also the data obtained recently with Drs. Boyd and Dworecki on the correlation of protein content to the TCPS in both groups of diseases, and summarized in Table 3, indicates that rather the reverse is true. The average content of serum proteins for the same level of thermal coagulation is only in one group (with a 3 plus increase in TCPS) higher in cancer than in non-neoplastic diseases, and in all other is lower. No evidence is obtained from this data to support the thesis of the existence of a specific defect in thermal coagulation of serum proteins in cancer patients.

It is obvious, therefore, that we cannot expect any better results with the Huggins technic than with the determination of the TCPS for cancer diagnosis. This is really the case, as shown by our data, obtained with Drs. Boyd and Dworecki based on 240 iodoacetate tests in as many individuals, including 50

TABLE 3

*Correlation of thermal coagulation point with total protein content of serum in cancer and non-neoplastic diseases*

THERMAL COAGULATION POINT OF BLOOD SERUM	NUMBER OF CASES STUDIED IN THE GROUP	AVERAGE TOTAL PROTEIN CONTENT IN SERUM IN GM. PER 100 CC.	
		Carcinoma of internal organs	Serious non-neoplastic diseases
°C.			
75-81	115	6.87	7.18
82-84	43	6.61	6.70
85-89	10	6.52	7.12
90-95	9	6.46	6.23
over 95	10	5.37	6.17

patients with malignancies, and 190 with non-neoplastic diseases of various kind, out of which 146 were selected among the group of illnesses prone to thermal coagulation defect. The results of these studies, which will be published in detail elsewhere (28) are summarized in Table 4.

The data listed in the Table 4 make it evident that the percentage of positive results in non-operated cancers is very low and amounts to 32.4 per cent only. The percentage of "false positive tests" in severe non-neoplastic diseases prone to thermal coagulation defect is very similar in the selected group of cases and amounts to 26.7 per cent. Pneumonia, pregnancy with infection or hemorrhage, severe non-neoplastic diseases of the digestive tract, the postoperative states shortly after laparotomy, and pyogenic processes give equal or often higher percentage of positive Huggins tests than cancers. Also cases of heart failure and pulmonary tuberculosis contribute to the non-specificity of the iodoacetate test. The results are as discouraging as could be suspected a priori on the basis of the determinations of TCPS in cancer and other diseases. They confirm the thesis that the principle of defective thermal coagulation of blood serum cannot be used for general cancer diagnosis.

In the diagnosis of cancer, the study of the thermal coagulation defect of serum seems to have only a limited diagnostic significance in those cases where there is a wide margin between its incidence in neoplastic as compared to non-neoplastic disease of the same organ. This happens in chronic diseases of digestive tract, as it was pointed out previously (19, 20).

In 85 cases of malignancy of the digestive organs (20) approximately 70 per cent have shown an increased TCPS (2-4 plus), whereas among 215 cases of non-malignant disease of these organs, this occurred only in about 20 per cent.

TABLE 4

*Incidence of positive Huggins test in 240 cases of neoplastic and non-neoplastic disease*

DIAGNOSIS	NUMBER OF CASES STUDIED	NUMBER OF POSITIVE TESTS	PERCENTAGE OF POSITIVE TESTS
<i>Neoplastic diseases:</i>			
Non-operated malignant tumors of abdominal organs, lungs, thyroid, prostate, breast and bones.....	37	12	32.4
Operated malignant tumors of same organs (examined within 2 weeks after operation).....	9	5	55.6
Successfully removed tumors (examined several months or years after operation).....	4	0	0.0
Total .....	50	17	34.0
<i>Non-neoplastic diseases:</i>			
Pneumonia.....	7	4	57.1
Ulcerative colitis, pyloric stenosis, obstructive jaundice (of long duration).....	5	2	40.0
Complicated pregnancy (infection, hemorrhage).....	14	5	35.7
Pyogenic processes .....	9	3	33.3
Postoperative states (after abdominal operations).....	39	13	33.3
Heart failure .....	17	4	23.5
Active pulmonary tuberculosis.....	55	8	16.4
(Total).....	146	39	26.7
Other miscellaneous diseases.....	44	5	11.4
Total.....	190	44	23.2

A normal TCPS was found about 3 times as often in non-neoplastic as in neoplastic diseases of digestive tract. On the other hand, a 2-3 plus increase was found about 3 times, and a 4 plus increase in TCPS—more than 7 times more often in cancer of digestive tract than in non-neoplastic disease of the same organs (20). In chronic non-pyogenic abdominal illness, after exclusion of ulcerative colitis, obstructive jaundice and severe pyloric stenosis, the defective thermal coagulation may be indicative of a malignant process in the abdomen.

Determination of the TCPS may also be useful in the differential diagnosis of ascites. The data obtained in 44 cases of ascites of various origin (19, 20) have

shown that ascites due to intraabdominal malignancy was associated with a definite increase of thermal coagulation point. The same happened however in ascites due to nephrosis, heart failure, and in a few cases of advanced hepatic cirrhosis with peripheral edema and hypoproteinemia. In early cirrhosis, without peripheral edema, normal TCPS was constant. Therefore in a patient with ascites a normal TCPS tends to exclude a neoplastic origin and suggests cirrhosis, while a defective thermal coagulation strongly indicates malignancy, if cardiac and renal factors can be excluded, and no other edema or transudation are present.

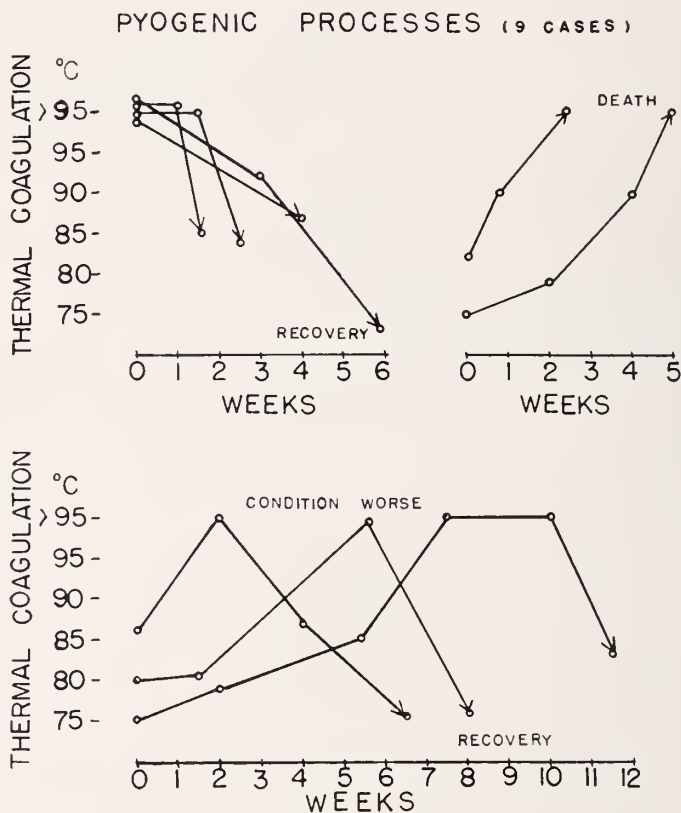


FIG. 1. Correlation of thermal coagulation point of blood serum to the course of disease in pyogenic processes of the chest, abdominal cavity and extremities.

Is there any other clinical application for the study of the defective thermal coagulation of blood serum outside of the problem of cancer diagnosis? We believe that there is one, and that the TCPS can be used as an easily performed non-specific serological indicator of severe illness.

The determination of the TCPS at various intervals in about 250 cases (19, 20) has shown that the TCPS represents a kind of serological correlate to the course of disease. It increases with deterioration, decreases with improvement, and reverts to normal with recovery.



In acute disorders, the increase in the TCPS is transient. It vanishes with improvement of the patient and provides only information concerning the stage of disease but not with respect to the gravity of prognosis of the underlying pathology. This is shown in Figure 1 which indicates changes in TCPS occurring in pyogenic processes; it swings up with advance of the disease and reverts to normal with improvement due to operation or antibiotic treatment. Cases, which are listed in the Figure 1 are: periappendicular abscesses, purulent peritonitis, purulent salpingitis and perimetritis, and cases of empyema, cellulitis and septic abortion.

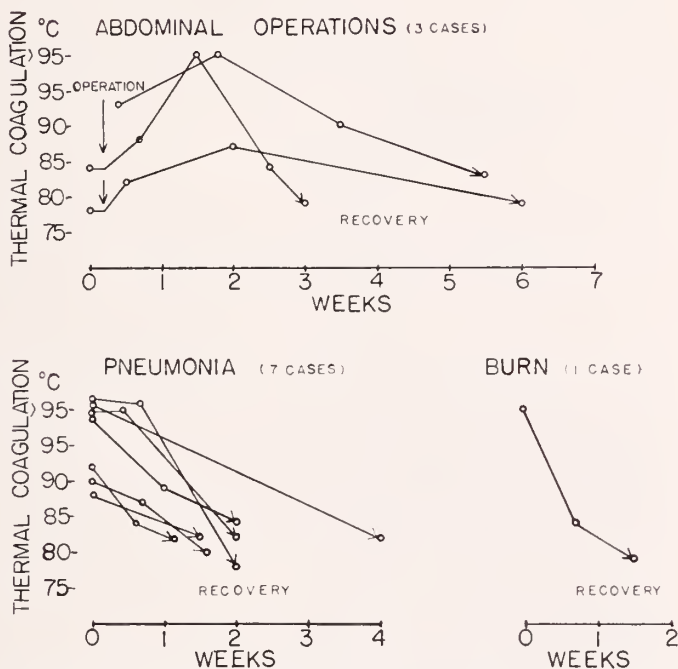


FIG. 2. Correlation of thermal coagulation point of blood serum to the course of disease in pneumonia, extensive burns and after abdominal operation.

Similar changes are noted in Figure 2, which lists a case of extensive burns, where the highly increased thermal coagulation fell to normal value shortly after recovery of the patient. The same situation prevails in pneumonia, in which a marked defect in coagulation present during the acute stage reverts to normal values with recovery.

The effect of abdominal operations on the TCPS also will be noted in this Figure. Shortly after operation the thermal coagulation point swings up, and gradually within the next weeks comes down to normal value. This observation has been also recently made by Huggins et al. (29), in respect to iodoacetate test.

In Figure 3 the TCPS in 2 cases of eclampsia is shown, in which it reverted to normal with delivery and the recovery of the patient. Also to be noted is the

change in thermal coagulation with the course of cardiac illness, its increase with further failure and approaching death of the patient and its drop to normal values, if the treatment has improved the heart condition. Since 75 per cent of patients with heart failure have shown altered TCPS, irrespective of its genesis, and since this is unusual and occurs in a small fraction of patients with a compensated heart disease (20), defective thermal coagulation in a cardiac patient

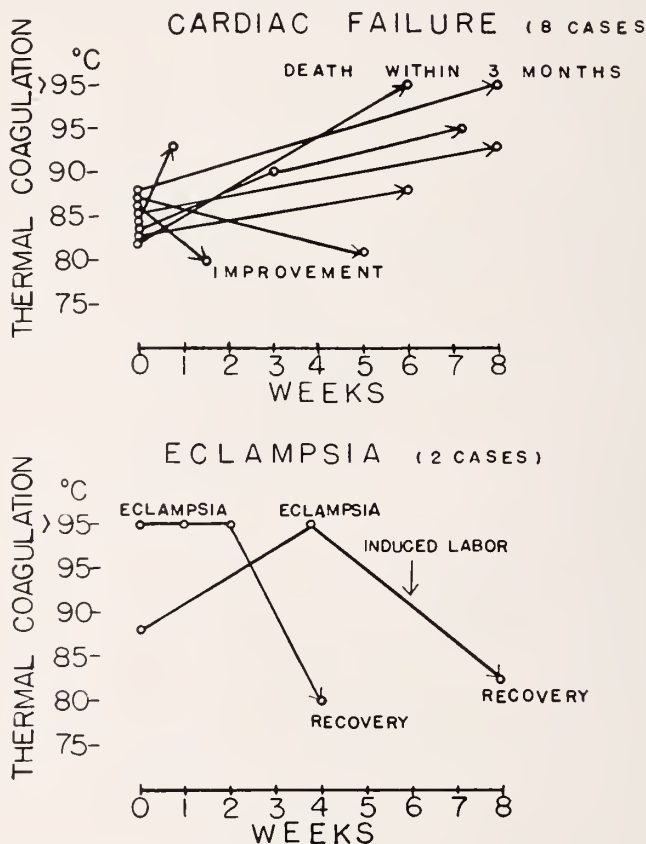


FIG. 3. Correlation of thermal coagulation point of blood serum to the course of disease in cardiac failure and eclampsia.

may indicate failure in the absence of another explanation. The heart which is damaged by a coronary lesion or hypertension may be associated with a normal TCPS.

In chronic and fatal diseases the level of TCPS indicates the gravity of the situation. In pulmonary tuberculosis the increase in TCPS occurs usually very late in the clinical course and its presence indicates an unfavorable prognosis. This is evident from Figure 4, which shows that the increasing TCPS signals the approaching death of the patient.

The defect in thermal coagulation increases also with the advance of the cancerous growth. It is an ominous sign as death soon follows (graphs in Fig. 4).



Table 5 shows the survival period in 45 patients with cancer who were followed for 1 year from the day of being tested. Among 13 cases of cancer showing a 2 or 3 plus increase in TCPS all but 2 died within 3 months after the initial test and out of 32 patients with cancer of the abdominal viscera showing a 4 plus increase

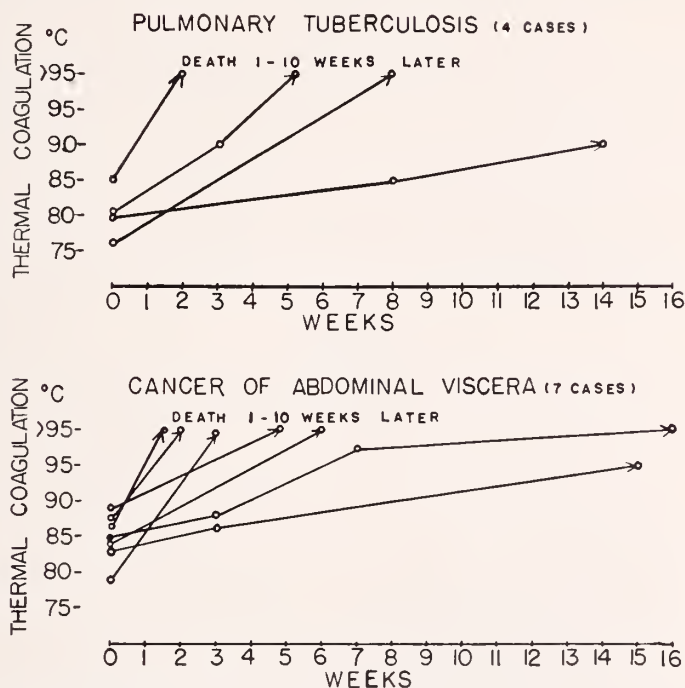


FIG. 4. Correlation of thermal coagulation point of blood serum to the course of disease in severe pulmonary tuberculosis and cancer of abdominal viscera.

TABLE 5

*Survival in 45 cases of carcinoma of abdominal viscera showing increased thermal coagulation point of blood serum*

DEGREE OF INCREASED THERMAL COAGULATION	NUMBER OF CASES	PERCENTAGE OF CASES WITH SURVIVAL TIME OF LESS THAN:		
		1 month	3 months	6 months
2 or 3 plus (84-95°C.)	13	0	61.5	100.0
4 plus (over 95°C.)	32	53.1	100.0	
Total	45	37.8	88.9	100.0

in TCPS one half died within 1 month and all died within 3 months from the date of performing the test. In all cases of malignancy with pronounced defect in thermal coagulation, the growth had extended widely by infiltration or metastases, has broken down, or has profoundly reduced general nutrition, as shown by hypoproteinemia and hypalbuminemia. Cachexia was not an essential feature as was reported previously (19). In all these cases the tumor was inoperable or

the postoperative survival time was short. If these findings are confirmed on a larger scale they may be of a definite prognostic value for predicting the survival time in patients with fatal disease, especially cancer. They may also serve as a guide in reaching a decision for surgical intervention when the problem of the operability of the tumor arises.

In general, the greater the defect in thermal coagulation the more grave was the condition of the patient. This will be evident from Table 6, which lists the results of the follow-up studies in 822 cases for 1 year after determination of the thermal coagulation of blood serum. It will be noted that the mortality in the group of cases with a 4 plus increase in TCPS was 8 times greater than that in a group of persons with normal coagulation. This is by no means intended to infer that the patient may not die soon with a normal thermal coagulation, or that the life expectancy in any disease can be made on the basis of thermal coagulation of serum. As was previously stressed, even the greatest defect in thermal

TABLE 6

*Mortality rate in 822 cases of miscellaneous diseases followed-up for one year after examination of the thermal coagulation point of blood serum*

GROUP NO.	THERMAL COAGULATION POINT OF BLOOD SERUM	NUMBER OF CASES EXAMINED IN THE GROUP	NUMBER OF DEATHS IN THE GROUP	MORTALITY RATE IN % IN THE GROUP
1	normal (75-80°C.)	383	32	8.4
2	increased 1 plus (81-83°C.)	145	24	16.5
3	increased 2, 3 plus (84-95°C.)	151	57	37.8
4	increased 4 plus (over 95°C.)	143	97	68.0
Total ...	.....	822	210	25.4

coagulation in acute diseases may revert to normal value within a short time, parallel to the recovery of the patient. On the other hand there are many severe diseases, like chronic glomerulo-nephritis with azotemia, coronary disease, severe hypertension, cerebral hemorrhage, poisonings, etc.—which do not show any defect in thermal coagulation of serum. The presence of defective thermal coagulation means the presence of definite serious organic illness, but not vice versa.

#### THERMAL COAGULATION OF SERUM AND SERUM PROTEINS

The information obtained by studies of the thermal coagulation of blood serum differs from that obtained with other non-specific serological tests, and parallels neither the sedimentation rate nor the serological flocculations tests (20).

The TCPS may be normal and moderately or highly increased while the sedimentation rate is normal, and *vice versa*, the sedimentation rate may be low, normal or high at the same level of thermal coagulation. Only in a small percentage of cases is there a concordance between a high sedimentation rate and high levels of TCPS; in most instances an absolute discordance prevails (20).

The lack of correlation between the sedimentation rate and the TCPS may be

explained by the fact that the sedimentation rate largely depends upon disturbances in plasma fibrinogen (30, 31). This does not influence the thermal coagulation, which is determined in serum. If parallel deviations in both tests occur these would depend rather upon existence of other disturbances in blood which influence the sedimentation rate and may cause or be associated with deviations in the thermal coagulation of blood serum.

The same is true for the relation between the TCPS and the Weltmann heat coagulation band, as shown by comparative data obtained from a study of 200

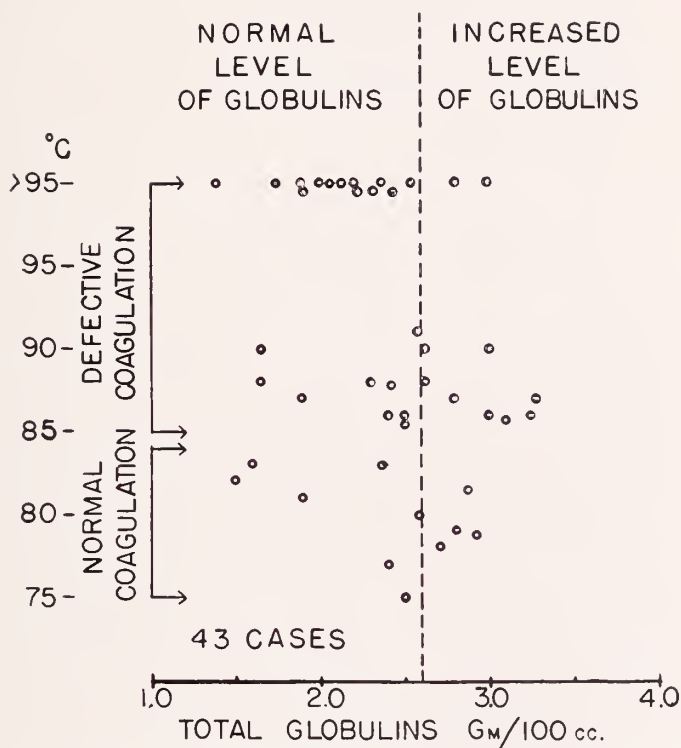


FIG. 5. Thermal coagulation point and total globulin content of the serum in 43 individuals with various disease.

sera (20). High and low values of TCPS were found at any values of the Weltmann test and *vice versa*. Only in about one half of the sera was some correlation obtained between the results of both tests. This difference in results is explained by the different mechanisms involved: the Weltmann test depends, like most of other flocculation tests, mainly upon the lability and increased content of *gamma*-globulin (euglobulin) fraction, whereas the TCPS does not show any relation to the content of serum globulins.

Figure 5 shows the correlation data on total globulins of the serum and the TCPS in the sera of 43 patients. The TCPS may be high or low with a normal content of globulin, and in cases of hyperglobulinemia no fixed defect of thermal

coagulation is seen. The subordinate role of globulins in production of defective thermal coagulation could be anticipated in view of the small hydration ability of globulins as compared to albumins, and also from the different incidence in disease of positive serological tests based upon globulin flocculation and defective thermal coagulation of serum.

We have as yet no data on the relationship of *alpha*- and *beta*- globulins to the level of the thermal coagulation point. The information available at present is entirely inadequate to determine the role of each of the serum protein fractions in the process of thermal coagulation. We do not know as yet what are the thermal coagulation points of protein fractions of the serum, isolated and purified by modern technics. We do not know what are the electrophoretic patterns of sera of patients showing defective thermal coagulation. This is certainly worth further study. Some preliminary data indicate the predominant role of albumins in this process (19, 20, 25, 26, 29).

The data from 400 simultaneous determinations of total serum proteins and TCPS in as many normal and pathological sera (20), and additional information obtained in a new series of 240 pathological sera (28), indicate that there is a general trend towards higher TCPS with lowering of the total proteins in the serum. In over 30 cases with a total protein content below 6.0 Gm. per cent, the TCPS was decidedly increased. This means that the hypoproteinemia is usually associated with defective thermal coagulation of blood serum. With a normal protein content, between 6.5 and 8.0 Gm. per cent, however, the TCPS may be low, normal, and moderately or highly increased, and there is no absolute correlation between total protein content and the thermal coagulation of blood serum.

The depletion of serum proteins is therefore one of factors of defective thermal coagulation of serum, but is not the only factor. Hypoproteinemia is most frequently associated with the depletion of serum albumins. This may indicate also the role of depletion of albumins in defective thermal coagulation of blood serum.

Figure 6 shows (in the form of a scatter diagram) the relationship of the TCPS to albumin content in the serum of 43 patients (20). It is evident from this graph that with depletion of albumins, the TCPS was practically always increased (in 21 sera out of 22 with albumin below 4.5 Gm per cent). With the lowest albumin levels (below 4.0 Gm. per cent) the TCPS was increased 4 plus in 10 out of 11 cases. This indicates the role of hypalbuminemia in the origin of defective thermal coagulation. Since the increase of TCPS was found in 9 out of 14 cases with normal albumin and globulin levels—the hypalbuminemia does not seem to be the sole reason for the thermal coagulation defect of the serum. This finding suggests a possibility of qualitative changes in serum proteins as an additional cause of defective thermal coagulation.

The role of qualitative changes in serum albumins as one of the factors producing defective thermal coagulation was considered 14 years ago (19) in relation to the general question of qualitative disturbances of serum proteins in disease (32, 33). The theory of qualitative disturbances in albumin fraction in disease was supported by studies on base binding power of electro dialysed serum

albumin, which was shown to vary from case to case under pathological conditions if calculated per unit of weight of albumin (34). Also other previous experimental data on the dye-binding power of albumin (35) seemed to point to the same theory, and especially important observations of Sobotka et al. (38, 39) and Brdicka (36, 37) on changes in the content of tyrosine and cystine in the amino-acid complex of albumin fraction under pathological conditions. Similar inferences concerning qualitative changes in albumins have been recently drawn

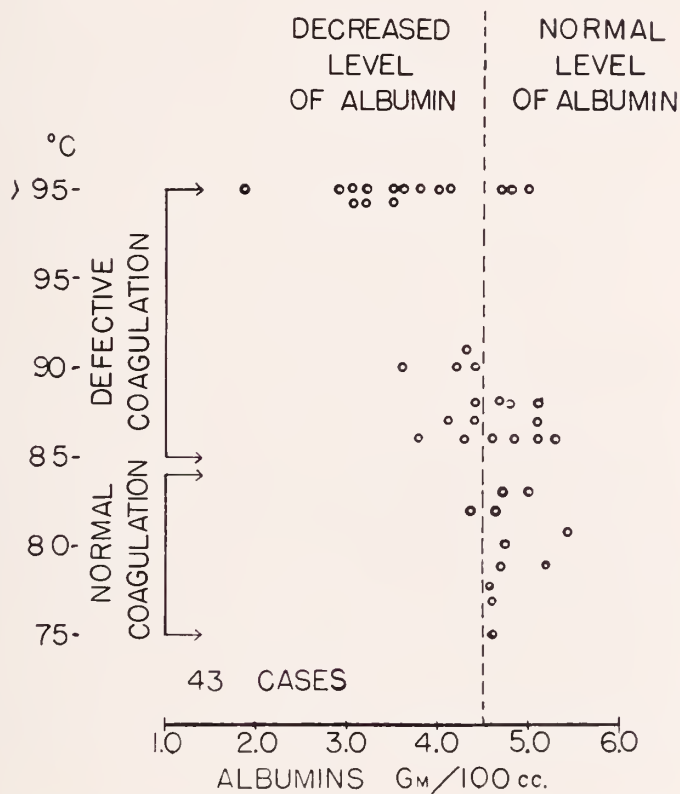


FIG. 6. Thermal coagulation point and total albumin content of the serum in 43 individuals with various disease.

(25, 26) and supported by data on binding of phenolsulphonephthalein to the albumin complex of serum (29) and the quantitative deficiency of one of the albumin fractions (albumin "A") in disease (40).

For this hypothetic qualitative disturbance in albumin complex of the serum we propose the name of "dysalbuminemia", to indicate the modification in the composition and properties of albumin in blood. In regard to thermal coagulation it would mean that the pathological process causes an alteration in the composition of the albumin complex, characterized by the preponderance of such fractions of albumin, which have the loosest micellar structures, the lowest inter-



micellar cohesion power, a stereo-structure least adapted to form a coherent gel, or the smallest water adsorption ability.

This abnormal albumin may partly be the labile "reserve albumin" from the tissues (41), a "young albumin" newly formed in the liver in excess, owing to the increased demand resulting from the protein loss of the body, or a "defective albumin" formed in the liver because of the impairment of albumin synthesis by some noxious agents. It may be also partly a product of albumin disintegration, related to proteose or mucoprotein-like components which enter the blood in increased concentration because of increased destruction of tissue proteins, as observed in cancer, pyogenic processes, tuberculosis, or burns (42-45). We do not know which of these possibilities or how many of them simultaneously cause "dysalbuminemia". Moreover, it must be kept in mind, that what to-day is called a qualitative change in albumin, to-morrow may be classified as a quantitative disturbance, and referred to as the shift in the mutual ratio of subfractions forming the albumin. The serum albumin may also turn out to be a complex of various fractions of different amino-acid composition and different physical constants, in the similar way as it is the case with serum globulin complex.

#### CONCLUSIONS

The incidence of defective thermal coagulation of serum in disease differs from that of most of other non-specific serological tests. This is due to its different mechanism and dependence upon quantitative and probably also qualitative changes in the serum albumins. For this reason it gives information which cannot be obtained by testing the sedimentation rate, protein content of the serum, or various flocculation reactions based upon disturbances in *gamma*-globulins of serum. Herein lies the main value of the test of defective thermal coagulation of serum, and because of this it may prove very useful as a diagnostic and prognostic aid within the frame of the entire clinical picture and in association with other laboratory data.

The thermal coagulation defect of serum may be detected by the simple technique of the determination of the thermal coagulation point of serum (TCPS) much easier than by measurement of the iodoacetate index with Huggins technique, and the information obtained is similar in significance.

The thermal coagulation point of blood serum follows to a great extent the course of disease and serves as an index of the severity of the underlying pathological process.

The defective thermal coagulation of blood serum, whatever its ultimate value, is not the principle upon which a reliable cancer test can be based. It has only a limited diagnostic value in some selected groups of malignancies, but it definitely does not belong to the cancer clinic and it cannot be applied to general cancer diagnosis and to screening of early cancer cases among the population because of the high incidence of false negative and false positive results.

The test based upon the principle of defective thermal coagulation should therefore not be called by the misleading name "blood tests for cancer". All available evidence indicates that defective thermal coagulation of blood serum, without



regard to the method by which it is tested, is a very useful but an entirely non-specific serological index of serious organic illness.

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## URINARY EXCRETION OF STILBAMIDINE AND 2-HYDROXYSTILBAMIDINE<sup>1</sup>

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Since the introduction of stilbamidine in 1939 (1) for the chemotherapeusis of kala-azar and trypanosomiasis, noteworthy results have been achieved in the therapy of kala-azar cases resistant to adequate courses of pentavalent antimony (2). In 1946 it was reported that the administration of stilbamidine to patients with multiple myeloma often caused a remission of bone pains, but that the final outcome was unchanged (3). Morphologic changes were noted in the myeloma cells of a considerable number of the patients receiving stilbamidine (4, 5, 6). These consisted in the development of basophilic particulate masses containing both ribonucleic acid (cytoplasmic nucleoprotein) and stilbamidine (7).

In 1948 it was reported that comparable changes of the myeloma cells were observed when patients were treated with 2-hydroxystilbamidine (8). The present paper deals with the urinary excretion of stilbamidine and 2-hydroxystilbamidine in these patients.

### METHOD

Stilbamidine diisethionate and 2-hydroxystilbamidine diisethionate were given by intravenous route, daily or every other day, starting the first day with a dose of 25 mg. and increasing to 150 mg. This report considers the results obtained following the 150 mg. dose only.

Twenty-one patients with multiple myeloma, a person who was recovering from dermatitis herpetiformis and two subjects with infections, were taken for study. The kidney function was not markedly impaired in these patients and relatively normal blood urea values were obtained (except myeloma patient 17).

The urine was collected in dark bottles (stilbamidine and 2-hydroxystilbamidine are photolabile in aqueous solution) for four hours and for the following twenty hours *on the day of injection*. The urine was sent to the laboratory immediately after collection. A 5 ml. aliquot was taken for determination of stilbamidine (9) and 2-hydroxystilbamidine (10) by the fluorophotometric methods developed in this laboratory. An adsorption-washing-elution procedure was employed having the advantages of objectivity, separation of stilbamidine and 2-hydroxystilbamidine from other fluorescent substances and optimal conditions for fluorimetric measurement of both compounds. Henry and Grindley described a spotting technique for the determination of stilbamidine in performance of which reliance is placed upon the visual matching of the fluorescence of spots (11). The authors admit that an error of 100% is possible when their method is

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used. We have tried this method and found large discrepancies due to the crudeness of the spotting technique (Table I).

TABLE I

*Values in Mg. for the Urinary Excretion of Stilbamidine\* As Determined By (A) Direct Spot Test,† (B) Measurement of the Fluorescence by Fluorophotometer after Separation from other Fluorescent Materials‡*

	A	B
1	5.2	5.1
2	28.4	11.8
3	5.3	2.8
4	8.5	2.2
5	7.6	5.3
6	7.4	3.1
7	14.5	12.5
8	13.4	7.2
9	13.5	4.8
10	13.3	4.1
11	2.0	2.5
12	10.6	3.6
13	9.3	3.7

\* Expressed as stilbamidine diisethionate.

† Henry, A. J. and Grindley, D. N. (11).

‡ Saltzman, A. (9).

TABLE II

*Excretion of Stilbamidine After I. V. Injection of 150 Mg. Stilbamidine Diisethionate (= 77 Mg. Stilbamidine Base)\**

DIAGNOSIS	UREA N	FOUR-HOUR EXCRETION			TWENTY-FOUR HOUR EXCRETION		
		Number of determinations	Average value	Average deviation†	Number of determinations	Average value	Average deviation†
Normal.....	NPN 28	3	3.2	0.6	3	7.8	0.1
Subacute bacterial endocarditis.....	8	1	4.3	—	1	6.6	—
Lupus vulgaris.....	NPN 20	3	2.9	0.3	3	5.6	0.9

\* All values expressed as stilbamidine base.

† Average deviation of a single determination, in mg.

## OBSERVATIONS

In Tables II, III, and IV, data on the urinary excretion of stilbamidine after intravenous injection of 150 mg. stilbamidine diisethionate (equivalent to 77 mg. stilbamidine base) are given. The normal subject (Table II) excreted an average value of 3.2 mg. of stilbamidine base (4.2 per cent) in 4 hours and 7.8 (10.1 per cent) in the first 24 hours. The two subjects with infections (subacute bacterial endocarditis and tuberculosis) excreted comparable quantities in 24

TABLE III

*Excretion of Stilbamidine after I. V. Injection of 150 Mg. Stilbamidine Diisethionate\* in Patients with Multiple Myeloma*

NO.	UREA N	FOUR-HOUR EXCRETION			TWENTY-FOUR HOUR EXCRETION		
		Number of determinations	Average value	Average deviation†	Number of determinations	Average value	Average deviation†
			mg.				
1	10	10	4.4	0.7	7	8.7	1.9
	24‡	3	0.2	0.1	2	1.5	0.05
2	14	11	2.7	0.7	8	6.5	2.4
		8§	1.5§	0.6	7§	4.4§	0.6
3	19	12	3.1	1.1	7	6.3	0.8
4	8	9	2.8	1.2	5	6.2	1.2
5	10	9	2.4	1.2	5	6.1	3.4
6	12	14	2.3	0.7	11	6.1	1.1
7	17	16	2.1	0.5	10	4.1	1.1
8	21	18	2.3	0.4	12	3.8	0.6
9	18	15	1.8	1.0	8	3.4	1.2
10	12	8	1.1	0.3	9	3.2	0.8
11	23	8	1.1	0.4	7	3.2	0.8
12	15	9	1.1	0.5	9	3.1	0.9
13	23	6	0.8	0.2	6	2.6	0.9
14	25	11§	0.6§	0.2	10§	2.2§	0.7
15	20	9	0.5	0.2	9	1.4	0.4
16	21	6	0.5	0.4	3	0.4	0.0
17	36	2	0.2	0.0	2	1.0	0.3

\* Equivalent to 77 mg. stilbamidine base. All values expressed as stilbamidine base.

† Average deviation of a single determination, in mg.

‡ Readmission six months later.

§ By intramuscular injection.

TABLE IV

*Day by Day Variation of the Excretion of Stilbamidine after Daily Intravenous Injection of 150 Mg. of Stilbamidine Diisethionate in a Patient with Multiple Myeloma*

DAY OF TREATMENT	24 HOUR EXCRETION OF STILBAMIDINE BASE
	mg.
I	5.3
III	6.2
IV	3.1
V	4.5
VI	8.3
VII	6.8
VIII	2.7
IX	4.2
X	4.4
XI	2.1
XII	3.5
XIII	6.7
XIV	4.6
XV	0.8
XVI	0.9
XVII	0.8
XVIII	1.1
XIX	0.6

\* Injections discontinued.



hours (6.6 mg. and 5.6 mg. respectively). In Table III, 17 patients with multiple myeloma are listed in order, depending upon the quantity of stilbamidine base excreted in the first 24 hours. It can be noted that the 4-hour values fit into this series in almost the same order. While between patients the variation in excretion ranges greatly (0.4 mg. to 8.7 mg. per 24 hours) the individual patient excreted stilbamidine at a fairly constant rate. The individual daily variations in excretion of stilbamidine in a single patient are illustrated in Table IV. In agreement with the results of Kirk and Henry (12) we found that after cessation of the injections the urinary excretion of stilbamidine immediately dwindles to values of about 1 milligram per 24 hours.

TABLE V

*Day by Day Variation of the Excretion of 2-Hydroxystilbamidine after Daily Intravenous Injection of 150 Mg. of 2-Hydroxystilbamidine in Two Patients with Multiple Myeloma*

CASE I			CASE II	
Day of treatment	Received in total	24 hours excretion of 2-hydroxystilbamidine base	Day of treatment	24 hour excretion of 2-hydroxystilbamidine base
	mg.	mg.		mg.
VIII	1200	4.3	I	2.3
X	1500	6.4	II	4.8
XII	1800	5.0	III	3.3
XIII	1950	7.9	VII	5.3
XIV	2100	4.7	VIII	8.8
XV	2250	6.8	X	2.5
XVIII	2700	2.7	XI	4.3
XXIII	3450	4.7	XII	4.6
XXIV	3600	6.2	XIII	4.2
			XIV	6.4
			XV	2.3
			XVI	7.1

Table V shows the excretion of 2-hydroxystilbamidine in two myeloma patients who received daily intravenous injections of 150 mg. The average daily excretion in these two patients was 5.4 and 4.6 mg. respectively.

#### DISCUSSION

A few observations have been made of the absorption, deposition and excretion of stilbamidine. In 1941, Hawking and Smiles found that stilbamidine injected into mice infected with trypanosomes was absorbed not only by the trypanosomes but was also deposited in the liver, kidneys and skin, and excreted in the urine (13).

One normal person and one kala-azar patient were studied by Henry and Grindley using the spot test method (11). After a single injection of 100 mg. of stilbamidine they found that about 10 per cent of the dose was excreted in the urine in the first few hours, after which only traces could be detected up to two days after injection. Our studies confirm the findings of Henry and Grindley as to the relatively small amount of stilbamidine which normal subjects excrete in



the urine. While making observations on the toxicity of stilbamidine in kala-azar patients, Kirk and Henry studied the urinary excretion of the drug in four patients with the spot test method (12). In two of the cases they noted a rapid increase in rate of excretion of the drug "until by the time the 7th or 8th injection is reached, the amount excreted over the two-day period is 75-85% of the amount administered." In contrast to this finding, we did not notice any grossly significant change in the rate of excretion in any one subject, although the excretion for as many as 18 consecutive injections was determined.

The excretion of 2-hydroxystilbamidine after intravenous injection is comparable to the excretion of stilbamidine.

#### SUMMARY

After intravenous injection of 150 mg. stilbamidine diisethionate, the urinary excretion of stilbamidine base in a normal subject was 4.2 per cent in four hours and 10.1 per cent in 24 hours. In most patients with myeloma, comparable values were found although in other myeloma patients much lower amounts of stilbamidine were excreted.

In two patients with myeloma the excretion of 2-hydroxystilbamidine diisethionate was followed after intravenous administration. The daily average excretion varied around 6 and 7 per cent of the quantity injected.

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## DIHYDROERGOCORNINE IN THE DIFFERENTIAL DIAGNOSIS OF FUNCTIONAL HEART DISTURBANCES AND ORGANIC HEART DISEASE\*

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Accurate differential diagnosis of functional heart disturbances and organic heart disease is not always possible with the clinical methods available. Even in the absence of pathologic changes in the heart, emotion may produce electrocardiographic abnormalities which are indistinguishable from those occurring in organic heart disease (1). Alterations in the electrocardiogram caused by emotional disturbances are often erroneously accepted as signs of cardiac involvement, and the patient is needlessly made a cardiac cripple. Furthermore, patients with functional cardiac disturbance or persons who are under unusual mental stress may have chest pain that not only simulates true angina pectoris but may even be relieved by administration of nitroglycerine. The effect of this drug, therefore, cannot be depended upon for differential diagnosis. Chest pain may also be the predominant symptom (2) in patients with functional disorders (anxiety states or neurocirculatory asthenia) or with chest lesions other than those due to cardiac disease. The results of tests made with dihydroergocornine lead us to believe that this drug offers a safe means for further study in differentiating functional and organic diseases of the heart.

It has been estimated that on initial examination of patients with coronary artery disease the results of all routine examinations, including physical and radiographic findings and the 12 lead resting electrocardiogram, may be normal in from 25 (3) to 37.3 (4) per cent of the cases. These figures indicate the possible diagnostic value of stress tests of the heart, such as the "2-step" exercise electrocardiogram and the 10 per cent oxygen test, in providing objective evidence of organic heart disease (5, 6). Unfortunately these two procedures cannot be used alone to distinguish organic from functional cardiac disturbances since even such objective tests may produce positive electrocardiographic alterations in patients with functional disorders. The abnormalities (RS-T depressions and T wave inversions) that occur with functional cardiac states may be as pronounced as those observed with organic heart disease so that differentiation cannot be made on a quantitative electrocardiographic basis.

Earlier attempts to find a method for obtaining accurate differential diagnosis utilized ergotamine tartrate (Gynergen-Sandoz) intravenously (7-9) but the angina-provoking properties of this drug in coronary artery disease precluded its routine use (9-10). Since June, 1948, our research has been conducted with dihydroergocornine (DHO-180)\*. It has been stated that dihydroergocornine (DHO-180), a dihydrogenated ergot alkaloid derived from ergotoxine, possesses

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sympathicolytic properties in man without the direct vasoconstrictive action on smooth muscle characteristic of ergotamine and dihydroergotamine (DHE-45) (11-21). Some investigators (22, 23) believe that DHO-180 lacks marked "sympathicolytic" properties, and state that the bulk of evidence favors either central depression of vasomotor reflexes and/or central vagal stimulation (23). In any event, even if the mode of action is controversial, our results with dihydroergocornine appear to be of clinical importance.

#### METHOD AND RESULTS

The tests reported here were made with dihydroergocornine used in conjunction with the "2-step" exercise electrocardiogram. The effect of intravenous administration of this drug on blood pressure, heart rate and electrocardiogram was determined in an earlier series comprising 116 subjects (24). These patients were given single intravenous injections of DHO-180, 0.5 mgm. in most instances. Onset of action of the drug took place within a few minutes following injection, and the duration of effect was over one hour. Only transient side effects of no serious consequence occurred.

The present group consists of twenty selected patients with signs and symptoms of cardiac disturbance in whom the "2-step" exercise test was performed, both before and following intravenous administration of dihydroergocornine. Eighteen patients received 0.5 mgm. and two patients 0.4 mgm. of the drug. On the basis of clinical signs and symptoms ten of the patients were classified as cases of functional heart disturbance and ten as cases of organic heart disease. The "2-step" exercise tolerance test before administration of DHO-180 was positive in all twenty patients. Alterations in the electrocardiograms made following exertion occurred most frequently in leads  $V_4$  and II.

In the ten patients with functional heart disturbance (table I) physical examination, teleroentgenogram of the chest, and fluoroscopic examination of the heart revealed no deviations from normal. Six of the patients gave histories of atypical angina pectoris, and one a history of typical angina. In three of these patients variable relief was obtained by administration of nitroglycerine. Symptoms common to all patients were tachycardia and premature beats with predominance of anxiety state, emotional instability, and cardiac neurosis. Six of the patients were men and four were women; their ages varied from twenty-eight to fifty-four years. The resting twelve-lead electrocardiograms (three standard limb leads, aVR, aVL, aVF and unipolar precordial leads  $V_1$  through  $V_6$ ) were normal. In one instance (case 2, table I) an electrocardiogram taken during a spontaneous attack of typical "angina pectoris" was normal. The anoxemia (10% oxygen) test was positive in two of the four cases in which it was performed; one of these positive anoxemia tests reverted to negative when repeated after reassuring the patient.

Following the "2-step" exercise, RS-T depressions and T wave inversions occurred in the electrocardiograms of the ten patients with functional cardiac disease. Three patients were given the single test, that is, the walk over the steps for  $1\frac{1}{2}$  minutes; seven patients were given the double test in which twice the

TABLE I  
*Dihydroergocornine (DHO-180) and the "2-Step" Exercise Electrocardiogram: Functional Heart Disturbance*

CASE	AGE	SEX	HISTORY	PHYSICAL EXAMINATION	DIAGNOSIS	CHEST X-RAY AND/OR FLUOROSCOPY	ELECTROCARDIOGRAM		RESPONSE TO NITROGLYCERINE	B.P.	"2-STEP" TEST		DOSE AND REACTION TO DHO-I.V.N.	ANOXYMIA TEST	REMARKS
							Resting	Spontaneous attack			Before DHO	After DHO			
1. B. A.	41	M	Atypical angina pectoris—several months	Neg.	Anxiety state	Neg.	Normal			110/68	Pos. RS-T <sub>1, 2, 4</sub>	Neg. (Necrosynphrine)	0.5 mgm. Stuffy nose; slight nausea. Postural hypotension	Neg.	Physician
2. M. T. (Fig. 1)	28	F	Angina pectoris—typical, frequent palpitation, and slight dyspnea—6 yrs.; cardiophobia	Neg.	Anxiety state; cardiac neurosis	Neg.	Normal	Neg.	Variable relief at first; none at present	120/80	Pos. RS-T <sub>1, 2, 4</sub>	Neg.	0.4 mgm. Headache; stuffy nose	Pos.	
3. S. S.	28	F	Atypical angina pectoris since age of 8 following accidental blow to chest; occasional palpitation	Neg.	Anxiety state	Neg.	Normal			120/75	Pos. RS-T <sub>2</sub> & 4	Neg.	0.5 mgm. Slightly dizzy; stuffy nose; weakness		Physician
4. M. B.	53	M	Atypical angina pectoris—6 months; almost constant pain unrelated to effort	Neg.	Neurocirculatory asthenia	Neg.	Normal		Usually no relief	120/80	Pos. RS-T <sub>1, 2</sub> & 4	Neg. (Necrosynphrine)	0.5 mgm. Slight nausea; postural hypotension	Neg.	
5. H. S.	39	F	Episodes of paroxysmal tachycardia for 23 yrs. Emotional instability; cardiophobia	Neg.	Anxiety state; cardiac neurosis	Neg.—small heart dynamic pulsations	Normal			130/80	Pos. RS-T <sub>2, 3</sub> & 4	Neg.	0.4 mgm. Slight stuffy nose; nausea & vomiting	Pos.	Anoxemia test negative after reassurance
6. J. E.	39	M	Atypical angina pectoris—1 year. "Lump," lower sternal region 3 mos.; pruritus ant—4 yrs.	Neg.	Anxiety state	Neg.	Normal			125/80	Pos. RS-T <sub>1</sub>	Neg.	0.5 mgm. Slightly dizzy on standing		

7. I. T.	43	F	Diagnosed as "Myocarditis" 6 months ago. Hypotension many yrs. Syncope	Neg.	Neurocirculatory asthenia	Neg.	Normal			100/55	Pos. T <sub>2</sub> , 4	Neg. (Neosynephrine)	0.5 mgm. Stuffy nose; postural hypotension	Physiol
8. H. A.	33	M	Premature ventricular beats—12 years	Neg.	Routine check-up	Neg.	Normal			110/80	Pos. RS-T <sub>1</sub> , 2 & 4	Neg.	0.5 mgm. Stuffy nose; malaise	
9. K. B.	34	M	Atypical angina pectoris—5 years	Neg.	Anxiety state	Neg.	Normal		Relief	120/65	Pos. RS-T <sub>1</sub>	Neg.	0.5 mgm. Severe nausea; headache; stuffy nose	
10. R. F.	54	M	Atypical angina pectoris—5 years—onset after death of mother due to coronary occlusion	Neg.	Cardiac neurosis	Neg.	Normal			140/80	Pos. RS-T <sub>1</sub>	Neg.	0.5 mgm. Weakness and perspiration on standing	



number of trips is performed in 3 minutes. When DHO-180 was administered intravenously and a period of from thirty to sixty minutes allowed to elapse before the "2-step" test was repeated, the exercise electrocardiograms taken at the end of this interval remained normal. Case 2, Table I, is characteristic of the group. The patient was a 28 year old woman suffering from severe anxiety state, cardiophobia, and a history of typical anginal seizures of seven years duration. Physical examination and x-ray examination of the chest showed no abnormali-

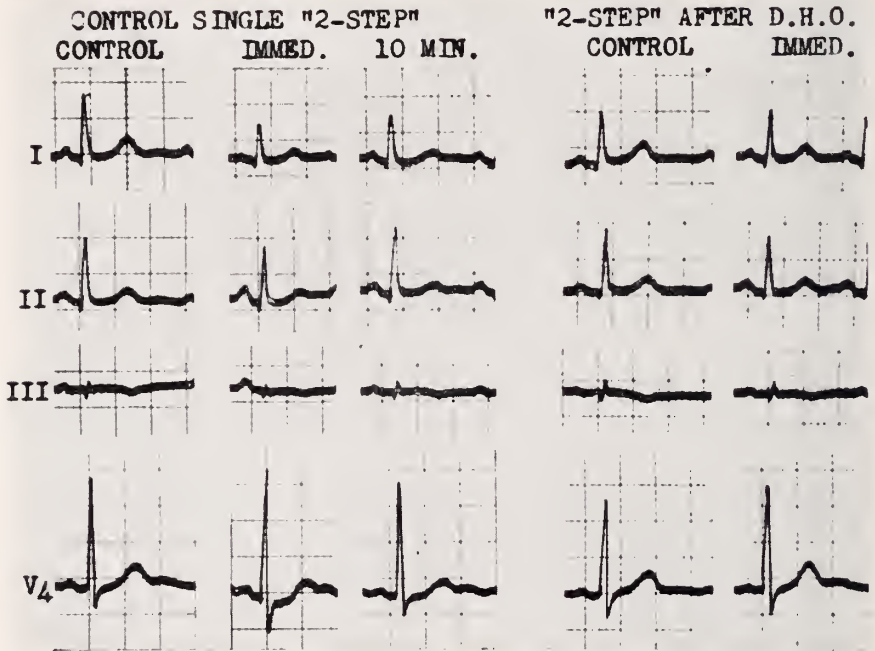


FIG. 1. (Case 2, table I) M. T., a woman, 28 years of age with severe anxiety state, cardiophobia, and typical angina pectoris. Physical examination and x-ray of chest were normal. The control electrocardiogram was normal, but immediately following the single "2-step" exercise, RS-T depression and notched T wave appeared in lead V<sub>4</sub>. The "2-step" exercise repeated thirty minutes after intravenous injection of dihydroergocornine (DHO-180) was negative.

ties. Nitroglycerine had afforded variable relief for a time, but subsequently injections of morphine were required to alleviate the pain. An electrocardiogram taken during a spontaneous attack of precordial pain was normal; the anoxemia (10% oxygen) test, however, was distinctly abnormal. Although the resting electrocardiogram was normal, single "2-step" tests were repeatedly positive: RS-T depression and notched T wave appeared in lead V<sub>4</sub> immediately after standard exercise with return to the normal control tracing after 10 minutes. However, when the "2-step" test was repeated thirty minutes after intravenous injection of dihydroergocornine (0.4 mgm), the electrocardiogram remained normal (fig. 1). During the many years that this patient has been followed, she has

not suffered any cardiac accident. The final diagnosis after psychiatric consultation was severe anxiety reaction with psychosomatic conversion.

The ten patients with organic heart disease (table II) gave unequivocal evidence of coronary artery disease. Nine of them had angina pectoris (typical or atypical), which was relieved by nitroglycerine in six cases. Four of the patients had previously sustained coronary occlusion with myocardial infarction and one suffered acute coronary insufficiency with congestive heart failure. The ten cases included six men and four women; their ages varied from 38 to 77 years. Five patients had hypertension. Four patients presented abnormal resting electrocardiograms. Left ventricular enlargement was demonstrated by teleroentgenogram and fluoroscopic examination in five of the cases. Electrocardiograms taken during spontaneous attacks of angina in three patients presented characteristic changes (Cases 2, 7, 9, table II). The anoxemia test was positive in three of the seven cases in which it was performed. Electrocardiograms made following the "2-step" exercise test were repeatedly abnormal in all ten cases; the single test was given in eight instances and the double test in two. Electrocardiograms taken in conjunction with the "2-step" exercise test performed thirty to sixty minutes following intravenous administration of dihydroergocornine (0.5 mgm), showed significant RS-T depression and T wave inversions similar to those noted in the control exercise tests. Case 2, table II, is a typical example of this group. A 38 year old man had a history of typical angina pectoris of one year's duration which was relieved by nitroglycerine. Physical examination, X-ray examination of the chest, and resting electrocardiogram failed to reveal any abnormalities. An electrocardiogram taken during a spontaneous attack of pain showed changes similar to those which occurred in electrocardiogram made following the single "2-step" exercise test, that is, marked RS-T depressions in leads  $V_4$ , I, and II. At a later time, the single "2-step" test was done thirty minutes following intravenous injection of dihydroergocornine (0.5 mgm.); the electrocardiogram showed RS-T depressions, similar to those that appeared in the earlier tracings. Subsequently, this patient presented intermittent periods of abnormal resting electrocardiograms and suffered increasing impairment of the coronary circulation with severe status anginosus, which led finally to cervico-dorsal sympathectomy. It is noteworthy that anoxemia tests on two separate occasions prior to the surgical procedure were negative.

In order to eliminate postural hypotension as a cause of alterations in electrocardiograms after the "2-step" exercise, the effect of standing on blood pressure, heart rate, and electrocardiogram was observed both before and following injection of dihydroergocornine. Prior to injection of DHO-180, standing did not produce a significant drop in blood pressure. Since DHO-180 possesses peripheral vasodilator properties, it was anticipated that hypotension on standing might occur following injection. Three patients with functional cardiac disturbance (Cases 1, 4, 7, table I) had marked hypotension with dizziness on standing, and one fainted. To enable these patients to perform the tests, a peripheral vasoconstrictive agent, Neosynephrin hydrochloride, 3 mgm., was injected intramuscularly. Since postural hypotension was thereby eliminated in these cases,

TABLE II  
*Dihydroergocornine (DHO-180) and the "2-step" Exercise Electrocardiogram: Organic Heart Disease*

CASE	AGE	SEX	HISTORY	PHYSICAL EXAMINATION	DIAGNOSIS	CHEST X-RAY AND/OR FLUOROSCOPIC COPY	ELECTROCARDIOGRAM		RESPONSE TO NITROGLYCERINE	B.P.	"2-STEP" TEST		DOSE AND REACTION TO DHO-I.VEN.	ANOXEMIA TEST	REMARKS
							Resting	Spon- taneous attack			Before DHO	After DHO			
1. S. G.	53	F	Angina pectoris—3 yrs. Diabetes mellitus—5 yrs.	Neg.	Hypertensive and arteriosclerotic heart disease; anginal syndrome	Left ventricular enlargement	Abnormal: RS-T depressed in V <sub>3</sub> & V <sub>4</sub>			170/95	Pos. RS-T <sub>4</sub>	Pos. RS-T <sub>4</sub>	0.5 mgm. Stuffily nose; slightly dizzy; nausea	Neg.	
2. S. I. (Fig. 2)	38	M	Severe angina pectoris 1 year	Neg.	Arteriosclerotic heart disease; anginal syndrome	Neg.	Normal	Pos.	Relief	100/70	Positive RS-T <sub>1,2,3,4</sub> T <sub>1,2,3,4</sub>	Positive RS-T <sub>1,2,3,4</sub> T <sub>1,2,3,4</sub>	0.5 mgm. Slight stuffy nose; slight nausea; dizzy	Neg.	Later: abnormal resting ECG; and status anginosus-symptomatic pathectomy done
3. M. L.	42	F	Angina pectoris—4½ yrs.	Neg.	Arteriosclerotic heart disease; anginal syndrome	Neg.	Normal		Relief	100/70	Positive Intraventricular block	Positive Intraventricular block	0.5 mgm. Stuffily nose; slight nausea	Positive Intraventricular block	Intraventricular block following exertion and anoxemia
4. R. G.	42	F	Hypertension for 2 yrs. Treated with rice diet; dull precordial pain with T wave changes	Hypertensive retinopathy—grade II	Hypertensive and arteriosclerotic heart disease; anginal syndrome	Left ventricular enlargement	Abnormal: T <sub>1</sub> diphasic			150/90	Pos. RS-T <sub>4</sub>	Positive RS-T <sub>4,2</sub>	0.5 mgm. Stuffily nose		
5. E. D.	56	M	Angina pectoris—3 yrs. Dyspnea, orthopnea and hypertension 10 years. Posterior infarction	Hypertensive retinopathy—grade II	Hypertensive and arteriosclerotic heart disease; anginal syndrome. old posterior infarction	Neg.	Normal		Relief	225/110	Pos. RS-T <sub>1</sub> T <sub>1,2,4</sub>	Positive RS-T <sub>1</sub> T <sub>1</sub>	0.5 mgm. Dry mouth		

6. H. J.	64	M	Typical angina pectoris after acute coronary occlusion 13 and 11 yrs. ago	Systolic murmur at apex and base	Arteriosclerotic heart disease; anginal syndrome; old coronary occlusion	Left ventricular enlargement	Normal		Relief	150/75	Positive RS-T <sub>1,2,3</sub>	Positive RS-T <sub>4,5,6</sub>	0.5 mgm. None	Pos.
7. E. T.	77	F	Angina pectoris—5 yrs. Dyspnea on exertion	Neg.	Arteriosclerotic heart disease; anginal syndrome	Neg.	Normal	Pos.	Relief	110/60	Pos. RS-T <sub>4</sub>	Pos. RS-T <sub>4</sub>	0.25 mgm. Slight stuffy nose; generalized warmth; slight headache	Pos.
8. B. M.	46	M	Atypical angina pectoris since posterior infarction 1½ years ago	Congenital clubbed fingers	Arteriosclerotic heart disease; anginal syndrome; old posterior infarction	Neg. (small heart)	Abnormal: small Q; deep Q; QS in aVF		Relief	130/80	Pos. RS-T <sub>4</sub>	Pos. RS-T <sub>4</sub>	0.5 mgm. None	Neg.
9. M. H.	63	M	Angina pectoris since acute coronary insufficiency with congestive failure 3½ years ago	Blowing apical systolic murmur	Hypertensive and arteriosclerotic heart disease; congestive failure; anginal syndrome	Left ventricular enlargement; aorta; Transverse heart	Abnormal: Intraventricular block	Pos.		165/85	Positive RS-T <sub>1,2,3</sub>	Positive RS-T <sub>4,5,6</sub>	0.5 mgm. Slight stuffy nose	Neg.
10. J. C.	55	M	Hypertension 14 yrs; acute anterior infarction 5 yrs. ago	Heart enlarged to left	Hypertensive and arteriosclerotic heart disease; old anterior infarction	Left ventricular enlargement	Normal			174/108	Pos. RS-T <sub>4</sub>	Positive RS-T <sub>4,2</sub>	0.5 mgm. Slight stuffy nose	



the tests were completed satisfactorily. In fact, several days later, one of these patients (case 7, table I) was able to accomplish the "2-step" test after administration of DHO-180 without the use of neosynephrine and still with a negative result.

Although most patients showed a decrease in heart rate following administration of DHO-180, significant bradycardia was not produced. The latter was therefore eliminated as a factor in the negative "2-step" tests after the drug in

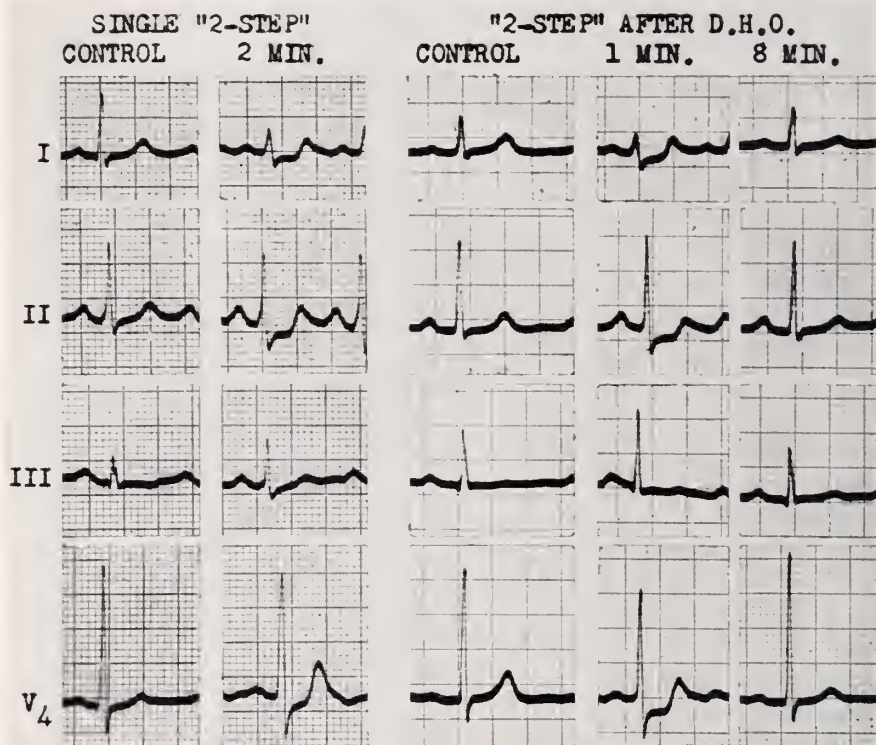


FIG. 2. (Case 2, table II) S. I., a man, 38 years of age with severe typical angina pectoris. Physical examination and x-ray of chest were normal. The control electrocardiogram was normal, but following the single "2-step" exercise, marked RS-T depressions appeared in leads  $V_4$ , I, and II. On a subsequent day, dihydroergocornine (DHO-180) was injected intravenously. The "2-step" test repeated thirty minutes later showed similar marked RS-T depressions.

the functional cases. Furthermore, the acceleration of the heart rate after exercise was such as to exclude marked tachycardia as a cause for positive tests.

#### COMMENT

Even in the absence of organic heart disease, emotionally unstable individuals may present electrocardiographic abnormalities such as pronounced RS-T depressions and T wave inversions spontaneously or during exercise and hypoxemia



tests. Attempts have been made to find a drug that may be used to prevent the appearance of these alterations. Ergotamine tartrate is contraindicated because of its angina-provoking properties. We have found that dihydroergocornine (DHO-180), in the dosage employed, is safe for the patient and appears to prevent electrocardiographic changes caused by functional disturbances, such as anxiety states.

The mechanism underlying electrocardiographic alterations in the RS-T segments and T waves of patients with functional heart disturbance has been discussed previously (9) and remains unknown. It has been suggested that the changes may be caused by actual diminution in coronary blood flow or by lability of the autonomic nervous system with resultant direct effect on the metabolism of the cardiac muscle and the properties of the membrane. Although the electrophysical explanations are unknown, DHO-180 appears to be a valuable agent for the study of the differentiation of organic and functional electrocardiographic changes. Further use of this drug is indicated for investigation of the relationship between the autonomic nervous system and the heart, with particular reference to the coronary circulation.

#### SUMMARY\*

1. Exercise electrocardiograms of patients with functional heart disturbance may have RS-T depressions and Twave inversions indistinguishable from those observed in organic heart disease.

2. The "2-step" exercise tolerance test was given to twenty patients before and following intravenous administration of dihydroergocornine (DHO-180). In ten patients with functional heart disturbance, the "2-step" test was positive before injection of DHO-180 but negative following the injection. In ten patients with coronary artery disease the "2-step" test was positive before and following injection of DHO-180.

3. Reactions produced by dihydroergocornine in patients with organic heart disease were not significant. The electrocardiographic abnormalities that occurred following exercise in patients with functional disturbances were prevented by the drug. Therefore dihydroergocornine (DHO-180) appears to be a safe and promising agent for further investigation in the differential diagnosis of functional heart disturbances and organic heart disease.

\* Since the completion of this paper, larger numbers of patients have been studied with the "2-Step" test both before and after administration of dihydroergocornine (DHO-180). The results in this larger series are now being analysed in conjunction with follow-up studies to determine the reliability of the method. In most instances, the differential diagnosis between functional heart disturbance and organic heart disease was obtained by this method, with occasional exceptions.

We are also extending our work to include a study of the effectiveness of C.C.K.-179 (a combination of dihydroergocornine, dihydroergocristine, and dihydroergokryptine) in the therapy of angina pectoris. This combination of dihydrogenated derivatives of ergotoxine is being essayed because of the supposed greater efficacy and lower incidence of side-effects.

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## EXCLUSION OF THE DOG HEART BY PARABIOSIS<sup>1</sup>

LESTER BLUM, M.D., AND SAMUEL J. MEGIBOW, M.D.

The rationale for shunting the blood stream about the empty heart has been presented by Gibbon (1) and others (2, 3). For this purpose, they have successfully employed a pump-oxygenator technic in the dog. Because of the numerous difficulties inherent in this method, we have developed a procedure in which a companion dog serves as the oxygenator, the blood exchange being maintained by a double pump.

### PRELIMINARY EXPERIMENTS

These can be divided into five groups. Dogs weighing from 12 to 20 kg. were the subjects. Veterinary nembutal (30 mg./kg. intravenously) was the anaesthetic agent. The "Pneophore" automatic pressure device (4) was used as well as an ordinary to and fro respirator. The amounts of heparin varied widely and, where indicated, protamine was used as a neutralizing agent. In the first group there were three experiments in short circuiting of the right heart. A Brewer automatic pipette was used as the pump and large bore needles as conduits into the venae cavae and pulmonary artery. It became obvious that the concentration of heparin necessary with this machine was so great that serious hemorrhage followed withdrawal of the needles.

In the second group there were nineteen experiments in which various types of major vessel shunt were performed. It was on the basis of this experience that the tubing and connections ultimately used in the parabiotic experiments were chosen. The problem of puncturing a major artery in a heavily heparinized animal was partially solved (5).

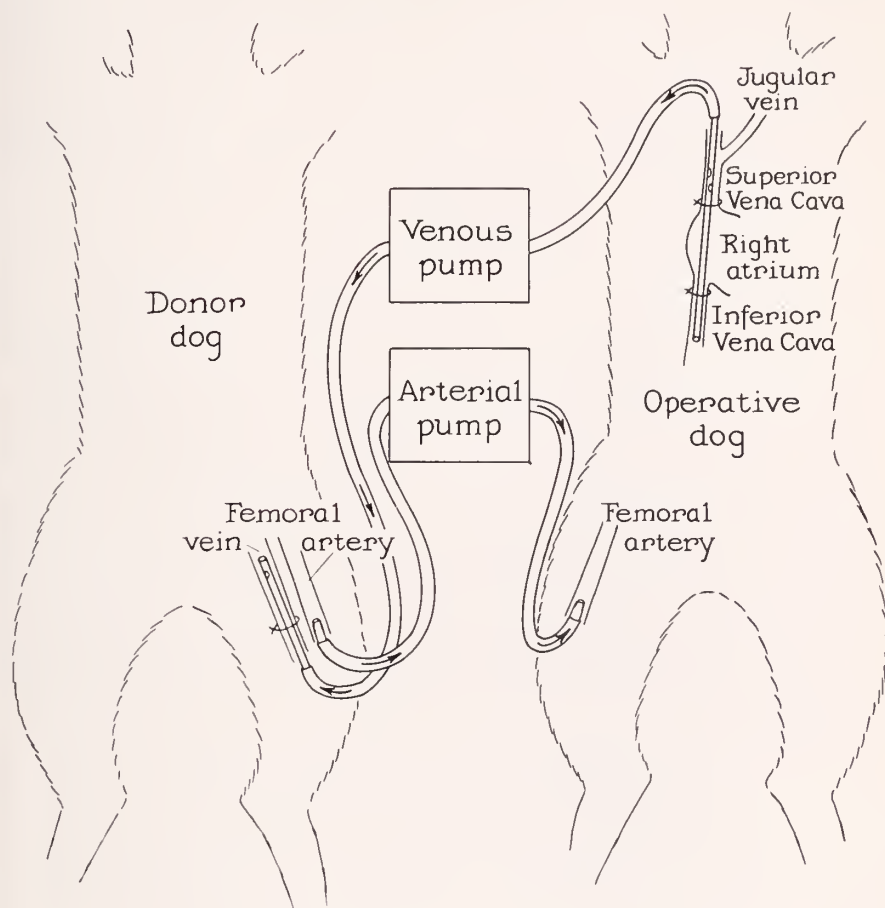
The third group of experiments was concerned with the development of a reasonably efficient and cheap oxygenator. A simple apparatus was constructed in which oxygen under pressure was led through a Berkfeld filter at the bottom of a thin plastic cylinder one inch in diameter and thirty inches high. As the minute bubbles rose through the column of blood they encountered a rim or baffle with an aperture which directed the unabsorbed bubbles into a hood. A layer of petrolatum overlay the small surface of the blood column. In this way bubbling and consequent foaming were minimized. This method was satisfactory for our purposes despite some hemolysis and considerable destruction of the leucocytes.

In the fourth group there were four acute experiments in which the heart was totally excluded for from ten to twenty minutes. The left ventricle was opened and found to contain little blood despite a mean aortic pressure of 120 mm. Hg. The coronary flow was sustained. This demonstrated that the aortic valves could keep the shunted blood from regurgitating into the left ventricle.

In the fifth group, there were five experiments in which a parabiotic method

<sup>1</sup> From the Laboratories of the Mt. Sinai Hospital, New York.

was first tried. It soon became evident that a balanced double pump was essential to achieve success. Our early attempts with one pump and a gravity transfer of venous blood failed. The venous blood of the operated dog was collected by



## Schema of Blood Flow in Parabolic Technic

FIG. 1. Arrangement of Animals

two catheters, one in each vena cava. This was later changed to the method described below.

### METHOD

Fredericq (6) is credited with being the originator of the parabolic technic. He cross-circuited the carotid vessels of two animals in order to study the effect on the brain. Numerous variations of this procedure have since been performed. In addition to direct vascular connections, the body cavities, trunk and extremi-



ties have been united in Siamese twin fashion to permit investigations in physiology and endocrinology.

In our method the auxiliary dog serving as the oxygenator is the active parabion. The dog whose heart is excluded is the passive parabion. To avoid confusion we have adopted a simpler, if less grammatical, terminology in which the auxiliary animal is labelled the "donor" dog and the other is called the "operative" dog, though there is an equal exchange of blood (fig. 1).

The dogs lie on parallel tables about thirty inches apart with the apparatus between. They are anaesthetized with veterinary nembutal (30 mg./kg. intravenously) and an endotracheal tube is inserted into the operative dog. The right jugular vein and right femoral artery of this animal are dissected out and cleared of tissue. The left femoral artery and vein of the donor dog are similarly treated.

An incision is made in the right fourth intercostal space of the operative dog down to but not through the pleura. All bleeding points are meticulously clamped and ligated. Both dogs are then heparinized with an average dose of 3 mgm./kg.

The tubing is given a final check for leaks and bubbles. A polythene catheter is introduced into the femoral vein of the donor dog and tied in place.

Lucite cannulas are inserted into the femoral arteries of both animals.

The right pleural cavity of the operative dog is entered and the automatic controlled respirator connected to the endotracheal tube. The lung is packed off and the azygos vein ligated. Silk ligatures are passed about the venae cavae close to their cardiac ostia. A large polythene catheter with appropriately spaced apertures is slipped down the previously prepared jugular vein in such manner that the openings lie in the superior and inferior venae cavae and all venous blood can be excluded from the heart by tying the caval ligatures about the catheter (7). The portion of the catheter in the right atrium between the ligatures has no openings.

As soon as the jugular catheter is properly placed the pumps are started. The venous blood of the operative dog is thus collected and passed through the venous pump to be introduced into the femoral vein of the donor dog. An equal amount of oxygenated blood is simultaneously pumped from the femoral artery of the donor dog back to the femoral artery of the operative dog. In this manner the circulation of the operative dog is maintained despite its empty heart.

#### APPARATUS<sup>2</sup>

Two pumps, identical in size and construction, constitute the apparatus (fig. 2). They are mounted with the remainder of the assembly on a steel frame set upon wheels. A  $\frac{1}{8}$  H.P. motor powers both through a sprocket chain.

The chamber of each pump is made of a dome of polished brass. Through its vertex a narrow stem leads off to serve as a bubble trap and pressure vent. The floor of the chamber is a solid sheet of tygon to the under surface of which is centrally attached a brass disc on which a lever acts. The other end of the lever is connected to an adjustable cam. The only valves are paired, synchronized stoppets which act externally on the tubing close to the vents.

<sup>2</sup> The apparatus was built by Walden Industries, New York.

The pumping action is mediated entirely through the rhythmic oscillation of the tygon membranes. Calibration and equilization of volume flow are controlled by adjustment of leverage on the cam as well as by the rate of the motor. The working capacity of this apparatus is adjustable from 300 to 700 cc./minute. Before use the pumps and tubing are carefully cleaned, chemically sterilized and equalized with an average volume error of less than 4 per cent. The tubing is of tygon of 4 mm. interval diameter. The only connections are at the pump vents and the cannulas. These are so arranged as not to narrow the lumen.

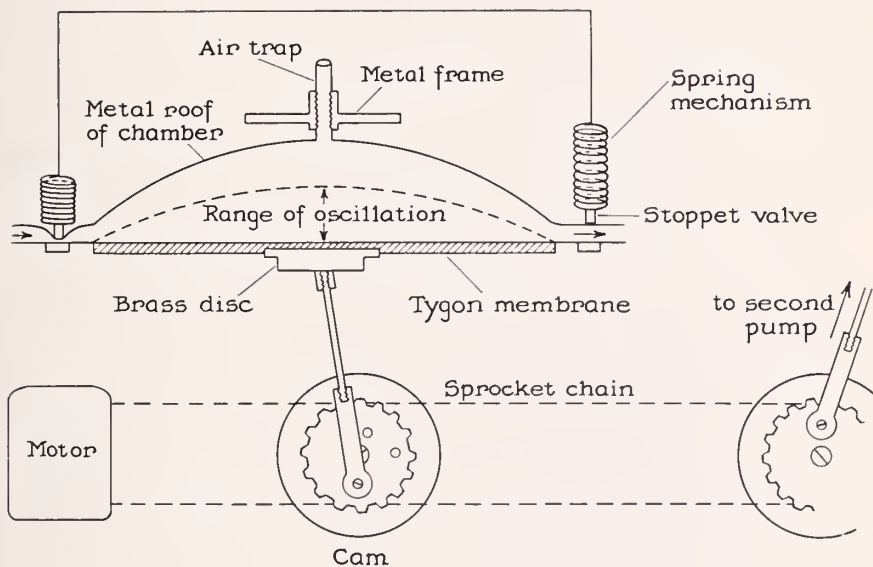


FIG. II. Schema of Apparatus

#### PROTOCOLS

*Proc. 53*—Operative Dog 15 kg; Donor Dog 35.4 kg. A total of 140 mg. of Heparin was used. The procedure followed the routine described above in every respect except that the right subclavian artery of the operative dog was cannulated instead of the right femoral artery. The heart was excluded for twelve minutes during which time it became quite small, flaccid and beat slowly but regularly. The apparatus ran at a rate of 700 cc./minute. When the catheters were removed the rate rose and the heart seemed to increase to larger than its original size. The dog expired at forty-eight hours. Post mortem examination revealed much blood in the mediastinum and pleural cavity. The apparent cause of death was shock due to hemorrhage. The donor dog recovered rapidly and completely.

*Proc. 54*—Operative Dog, 21.5 kg; Donor Dog 23 kg. A total of 120 mgm. of Heparin was used. The routine procedure was followed. Five cc. of 2 per cent procaine was injected into the pericardial sac in divided doses. The heart of the operative dog was excluded for fifteen minutes. The apparatus ran at a rate of 500 cc./minute. Both animals survived and did well.

*Proc. 55*—Operative Dog 11 kg; Donor Dog 23 kg. A total of 120 mgm. of Heparin was used. The routine procedure was followed. The heart of the operative dog was excluded for thirty minutes, the apparatus exchanging 700 cc./minute. Everything went smoothly with good recovery of the heart as it was allowed to fill. As the thorax was about to be closed, fatal ventricular fibrillation suddenly supervened.

*Proc. 56*—Operative Dog 13 kg; Donor Dog 18 kg. A total of 90 mgm. of Heparin was used. In order to inhibit irregularities, 0.050 Gm. of D.H.O. 180 was given intravenously. The routine procedure was performed. The heart of the operative dog was excluded for twenty-five minutes. It behaved well as the apparatus exchanged 500 cc./minute. To reduce the necessary circulating volume, tourniquets were applied to the extremities of the operative dog. The animal did well until its sudden death six weeks later. Autopsy revealed that an abscess in the thigh had perforated the femoral artery with resultant fatal hemorrhage. The donor dog died several days after. Autopsy disclosed an empyema secondary to a deep wound suppuration from a previous operation.

#### COMMENT

Despite the crude nature of this initial apparatus, the parabiotic method is evidently a feasible procedure. It is significant that only one death occurred on the operating table. This might have been avoided if procaine had been used. None of the four donor dogs died as a result of the procedure. The only mortality was quite evidently due to suppuration from an unrelated, prior operation.

The chief disadvantage of this method is that it places another animal in jeopardy. There are, however, a number of advantages over the pump-oxygenator technic. Most important is the lessened need for heparin. Because of the smaller volume of the apparatus and the quicker passage, a given unit of blood in the parabiotic method spends less time outside the normal endothelial channels than it does in an oxygenator. Furthermore, the lungs of the donor dog serve as the ideal filter since they remove the smallest of emboli without defibrination.

The efficiency of the lungs as an oxygenator and the normal reserve of the donor dog's heart readily allow an assumption of the additional burden imposed by the diverted blood of the operative animal. The circulating volume is cut down by the application of the tourniquets to the latter's extremities so that its blood circuit consists only of the vasculature of the head, the abdomen and the coronary vessels.

Further studies in progress include mechanical improvement in the apparatus, analysis of blood changes and estimation of blood volume requirements.

#### SUMMARY

A feasible parabiotic method of excluding the heart is described.

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## ANOTHER OCCUPATIONAL MARK\*

HOWARD T. BEHRMAN, M.D.

Within the past few years, there have been listed an increasing number of cutaneous changes which have been recognized as occupational stigmas. The well-trained dermatologist has become quite proficient in the use of occupational marks and signs as a guide to personal identification. The recent book by Ronchese<sup>1</sup> is an excellent summary of these signs.

The foregoing is a description of another occupational mark, hitherto unrecorded in the literature.



FIG. 1. Hyperkeratotic plaque between third and fourth fingers of right hand

### REPORT OF A CASE

K. G., a 46 year old white man, was admitted to The Mount Sinai Hospital in September, 1948 for the treatment of a hypertensive condition. While in the ward, it was noted that the skin between the middle and ring fingers of both

\* From the Department of Dermatology, The Mount Sinai Hospital, Service of Dr. Samuel Peck.

<sup>1</sup> Ronchese, F.: Occupational Marks and Other Physical Signs. Grune & Stratton, New York, 1947.



hands was lichenified (figs. 1 & 2). Closer examination revealed pea-sized, hyperkeratotic papules with slight surrounding erythema and scaling of the skin.

Further study of this patient disclosed the fact that these lesions had been present for twenty years. He ascribed them to his occupation as a textile worker. His particular type of work consisted primarily of pulling a slightly rough fabric through the involved fingers of both hands in order to test for impurities, flaws or unusual roughness of the material. This procedure was performed throughout the entire working day.



FIG. 2. This photograph illustrates the manner in which fabrics are handled in this type of textile occupation.

In confirmation of the diagnosis, several other facts were also ascertained. The patient's father, who had done similar work all his life, had the identical lesions in the same areas on both hands as did several fellow workers. The patient also observed that the involved areas practically disappeared when on vacation and while in the hospital but flared up following his return to work.

#### SUMMARY

This case herein reported presents another occupational mark which may be considered characteristic of exposure to one type of textile fabric.

# A NEW APPROACH TO THE ROENTGEN THERAPY OF CANCER WITH THE USE OF A GRID\*

(PRELIMINARY REPORT)

HIRSCH MARKS, M.D.

*Radiotherapist, New York City, Cancer Institute*

The dose of radiation that may be delivered to a tumor at any depth from the skin is limited, among other factors, by the tolerance of the skin. A method to increase the tolerance of the skin so that a much greater dose can be given than is possible by the usual methods of radiation therapy has been developed by a technique of irradiation through a grid. Grids employed in this method are perforated sheets of lead rubber with square apertures ranging from 0.25 cm.<sup>2</sup> to 4 cm.<sup>2</sup>. These apertures allow 40% transmission through the portal and they are distributed evenly over its surface in a chessboard pattern.

The grid is placed directly on the skin over the treatment field. In the technique used in the following three cases, higher air doses of x-ray are delivered through the grid than are employed in conventional x-ray therapy. The grid is applied so that the same areas of skin exposed by the apertures are irradiated at each treatment throughout the entire course of therapy.

Grids have been described previously by Kohler, Liberson, Haring, Grynkrant, and Jolles, but not with the dosage plan indicated in the following cases.

## ILLUSTRATIVE CASES

*Case 1.* B. E., a housewife, aged 53 years was admitted to the New York City Cancer Institute on May 18, 1948, complaining of a bleeding mass at the entrance of the vagina. Examination revealed an ulcerated, bleeding mass involving the vaginal vestibule and the lower halves of the labia minora. In the left inguinal region there were several small lymph nodes and a larger node about 3 cm. in diameter adherent to the underlying tissue. There were also shotty nodes in the right inguinal region which were not considered clinically significant. A biopsy from the vulval mass was reported by Dr. Angelo Sala, Pathologist, to be squamous cell carcinoma.

On May 20, 1948, conventional x-ray therapy was directed to the vulva through a 6 x 8 cm. portal. The daily dose was 200 roentgens in air; the total dose was 3000 roentgens in air over a period of 20 days. Physical factors were 0.9 mm. Cu. Half Value Layer and 50 cm. T.S.D. Treatment was completed on June 10, 1948. There was marked reduction in the size of the tumor. The patient returned to her home to be followed at regular intervals in the Clinic.

Re-examination on June 25, 1948, showed persistence of disease. Because of the failure of previous conventional radiotherapy, radiation through a grid was started. X-radiation to the vulvar lesion through a 10 x 15 cm. lead-rubber grid, 3 mm. in thickness, with fifteen 2.0 x 2.0 cm. openings, was instituted on June 25, 1948. Six hundred roentgens in air were delivered three times a week; the total dose was 7,800 roentgens in air. The quality of radiation was the same as was used in the previous conventional therapy. Treatment was completed in thirteen treatment days over a period of six weeks, ending on August 14, 1948.

\* Presented at the Tumor Clinic Conference, The Mount Sinai Hospital, N. Y., March 30, 1950. Portions of this presentation were read at the American Medical Association Convention, Atlantic City, N. J., June 10, 1949.

There was severe epithelitis of the vulva as well as epidermitis of the surrounding skin area. These reactions subsided within nine weeks after completion of treatment.

On February 17, 1949, six months after treatment, examination revealed no evidence of malignant disease in the vulva. A metastatic mass, hard and nodular and adherent to the underlying tissues, was palpated in the left inguinal region. It measured 8 x 10 cm. Aspiration biopsy from this mass was reported to be metastatic squamous cell carcinoma (Dr. Sala).

X-radiation through a 10 x 15 cm. lead-rubber grid, 3 mm. in thickness, with fifteen 2.0 x 2.0 cm. openings was instituted to the metastatic mass in the left inguinal region on February 17, 1949, and was completed on May 17, 1949. Six hundred roentgens in air were delivered three times a week; the total dose was 21,000 roentgens in air. Treatment was completed in thirty-five treatment days over a period of twelve and a half weeks.

Desquamation and denudation of the skin over the treated area appeared three days after completion of treatment.

On March 30, 1950, examination revealed absence of the posterior half of the labia minora with telangiectasia of the mucous membrane. The left inguinal region was free of metastases. There were areas of depigmented skin corresponding to the irradiated portals in the grid. Twenty-one months after radiation of the vulva and ten months after radiation of the inguinal mass, there was no clinical evidence of tumor.

*Case. 2.* R. J., a man, aged 77 years, had frequency and bleeding on urination since November, 1946. For six months he was treated with prostatic massages and injections of testosterone. On May 15, 1947, he was admitted to The Mount Sinai Hospital with acute urinary retention (residual urine 22 ounces). Intravenous urogram showed marked left hydronephrosis. Retrograde cystogram demonstrated a mass in the floor of the bladder. Exploration of the bladder through a suprapubic cystotomy on May 27, 1947, showed a large, mushy tumor of the bladder, pieces of which were removed digitally. This tissue was reported as papillary carcinoma of the bladder. On June 14, and June 25, 1947, portions of the tumor on the roof, lateral walls and floor of the bladder were removed by transurethral resection.

The patient was discharged from the hospital July 16, 1947, and returned on November 10, 1947 and May 6, 1948 for further transurethral resections of the bladder tumor. Biopsy still showed fragments of papillary carcinoma.

During the next 18 months, the growth of carcinoma was controlled by frequent transurethral resections. In February, 1949, a biopsy showed a change in the nature of the tumor. At this time, invasion of the muscle was observed in the biopsy specimen.

In November, 1949, extravesical extension of the tumor was observed. A suprapubic ventral hernia had developed, and within its ring a hard mass 5 x 7 cm. in its diameter was palpable just below the skin. Because of the extension of the tumor radiotherapy was considered indicated.

X-radiation was begun on November 8, 1949, through a 6 x 8 cm. lead-rubber grid directed to the suprapubic mass. The grid contained twenty 1 x 1 cm. holes. The daily dose was 1500 roentgens in air; the total dose was 24,000 roentgens in air delivered in 18 treatments over a period of 24 days. Physical factors were: 0.9 mm. Cu. Half Value Layer and 50 cm. T.S.D.

Seven days after the completion of treatment there was a wet desquamation of the skin which epithelialized in ten weeks.

On March 30, 1950, four months following completion of therapy, there was noted moderate atrophy of the skin in the treated field. The patient's general condition was good, and he was free of pain and urinary complaints.

*Case. 3.* J. G., a waiter, aged 67 years was seen by a dentist in July, 1949 because of a complaint of pain in the right side of his mouth on eating. His dentist found an ulceration of the tongue which was biopsied and reported as epidermoid carcinoma (Dr. Sala). The patient was referred to the Radiotherapy Department of the New York City Cancer Institute on July 21, 1949.

On examination there was a punched-out ulceration 2 cm. in diameter on the right lateral border of the tongue in its posterior third. The edge of the ulcer was indurated and the base was necrotic. The over-all diameter of the lesion was about 3 cm. X-ray examination of the mandible showed no abnormality. The patient was edentulous. There were no palpable lymph nodes in the neck.

X-radiation through a lead rubber grid 6 x 8 cm. in size, 3 mm. in thickness, with twenty 1 by 1 cm. openings was instituted on July 21, 1949. The grid was placed on the right cheek. This external right oro-pharynx field included the ramus and angle of the mandible in the beam. Radiation quality was 0.9 mm. Cu. Half Value Layer, 50 cm. T.S.D., 20 M.A., and 40 r/p.m. Twelve hundred roentgens in air were delivered daily. On August 5, 1949, 13,400 roentgens in air had been delivered and severe dysphagia necessitated interruption of treatment. Treatment was resumed September 14, 1949 and completed October 7, 1949. Upon completion 24,200 roentgens in air had been delivered in 20 treatment days over a period of 78 days.

Severe epithelitis of the tongue, buccal mucosa, and soft palate developed one week after completion of treatment. The wet desquamation of the skin in the treated area and the mucositis subsided ten weeks after therapy.

March 30, 1950, five months after treatment, there was no evidence of malignant disease in the tongue. The site of the original lesion was scarred, but soft. The skin was moderately atrophic.

#### COMMENT

These cases have been demonstrated because of their good early response to radiation by a technique not heretofore employed. By means of the grid technique unusually large doses of radiation as measured in air have been delivered to the skin. In spite of the large doses of radiation, the skin has healed completely, and there has been clinical disappearance of the underlying tumor.

#### DISCUSSION

*Dr. William Harris:* I have examined these three cases and have found no gross evidence of disease. The skin healed well with only slight atrophy such as is seen in conventional radiotherapy. This preliminary report suggests that further trial of the method should be made, for it shows great promise.

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## DEPTH DOSE CURVES FOR TREATMENT GRIDS IN RADIOTHERAPY\*

ROBERT LOEVINGER, Ph.D., AND WILBERT MINOWITZ, B.E.E.

The use of treatment grids, of the type discussed by Dr. Hirsch Marks in the preceding paper, requires depth dose information not given in the conventional depth dose tables. It is the purpose of this note to show that correct depth dose information can be derived from these tables.

Measurements will be reported here for two grids made by us: a 2-cm. grid (1.8 x 1.8 cm. openings in a 2 cm. checkerboard array), and a 1-cm. grid (1.0 cm. diameter holes located in a 1.4 cm. rectangular array). Both grids have 40% open area, and are made of 4 mm. lead rubber. The X-ray beam was generated by a Villard circuit, 200 Kvp, added filtration of 0.38 mm. Cu. plus 1 mm. Al., giving a HVL of 0.95 mm. Cu. The lead rubber attenuates this beam to 1.8%. The measurements were made at 50 cm. FSD, with a 10 x 15 cm. lead-lined cone which has a limiting aperture at the phantom surface.

All measurements were made in an infinite water phantom (1). The collecting volume of the ionization chambers was 4.5 mm. in diameter and 9.5 mm. long. These chambers were calibrated with a Victoreen R-meter, and are essentially wave-length independent. The chambers are of the direct current-reading type, and are used with a Beckman Ultrahmeter (full scale sensitivity  $2 \times 10^{-13}$  amp.) as the electrometer.

The depth dose at any point in tissue during treatment can be considered to be made up of two parts, one due to the primary beam, and the other to scattered radiation. Figure 1 shows the method of making this analysis for a conventional 10 x 15 cm. field. The uppermost curve shows the usual depth doses which, as shown, are essentially the same as those obtained in any of the published depth dose data (2, 3). The actual values shown represent our depth dose measurements combined with Quimby's backscatter value of 39.5% for this beam (2). The depth doses due to the primary beam alone are given by the lowest curve, which shows exponential attenuation with a half-value thickness of 3.22 cm. of water. This value is taken from our measurements for very small fields (1), and is in good agreement with the value given by the English workers (3). The difference between the total and the primary depth doses must be equal to the depth dose due to scattered radiation, which is plotted in the middle curve of the figure.

The total scattered radiation at the center of a 10 x 15 field covered by a grid with 40% open area, must be just 40% of the scattered radiation due to a full 10 x 15 field. This is shown as the solid line in Figure 2. Also shown are the experimental measurements of the depth dose behind a closed part of the grid. These measurements have been corrected for grid transmission by subtracting from each 1.8% of the primary intensity at that depth.

It should be noted that the computed scatter curve is 40% of the scatter due

\* From the Physics Laboratory and the Department of Radiotherapy, The Mount Sinai Hospital, New York, N. Y.



to a 10 x 15 field, and *not* the scatter due to a field 40% of 10 x 15, which would be 60 cm.<sup>2</sup> This latter field, being on the average closer to the central axis than a 10 x 15 field, gives more scattered radiation.

Figure 3 shows the computed depth dose curve under an open grid area. This is formed by adding the curve of Figure 2 to the primary beam curve of Figure

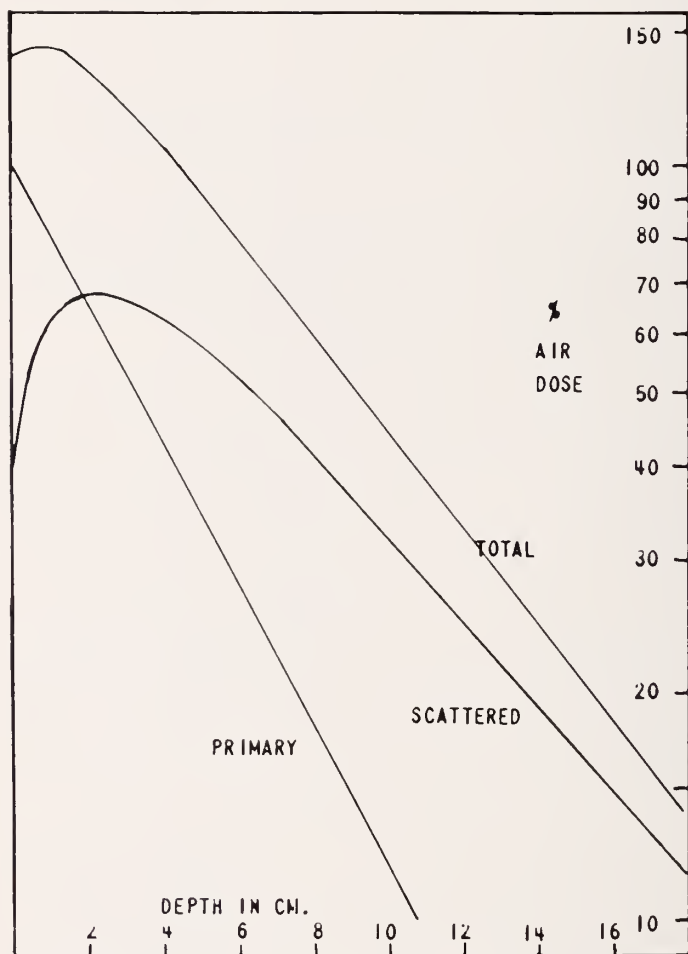


FIG. 1. Analysis of depth dose curve for 10 x 15 field, 50 cm. FSD, 1 mm. Cu. HVL. The top curve is a conventional depth dose curve. The straight line represents the depth dose due to the primary beam. The middle curve is the difference, representing the depth dose due to scattered radiation.

1. Also shown are the experimental points representing measurements behind the open areas. The agreement between the observed and computed values are excellent except for the first 3 cm. The reason for the differences between the observed and calculated values in the first 3 cm. is not known. Possibly it is experimental in origin. In any event, the method of analysis illustrated is apparently

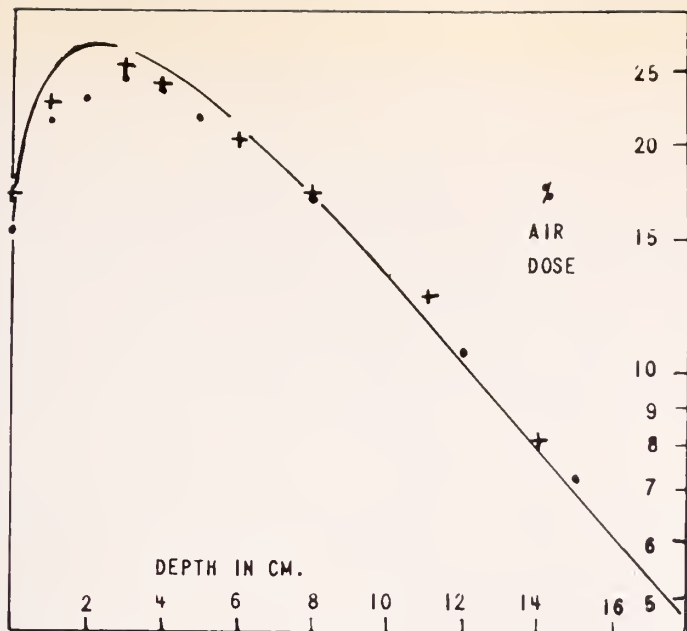


FIG. 2. Scattered radiation depth dose for treatment grids. The line is 40% of the scattered radiation curve of Figure 1. The dots and crosses represent measured depth doses behind a closed area of the 2-cm. and 1-cm. grids, respectively.

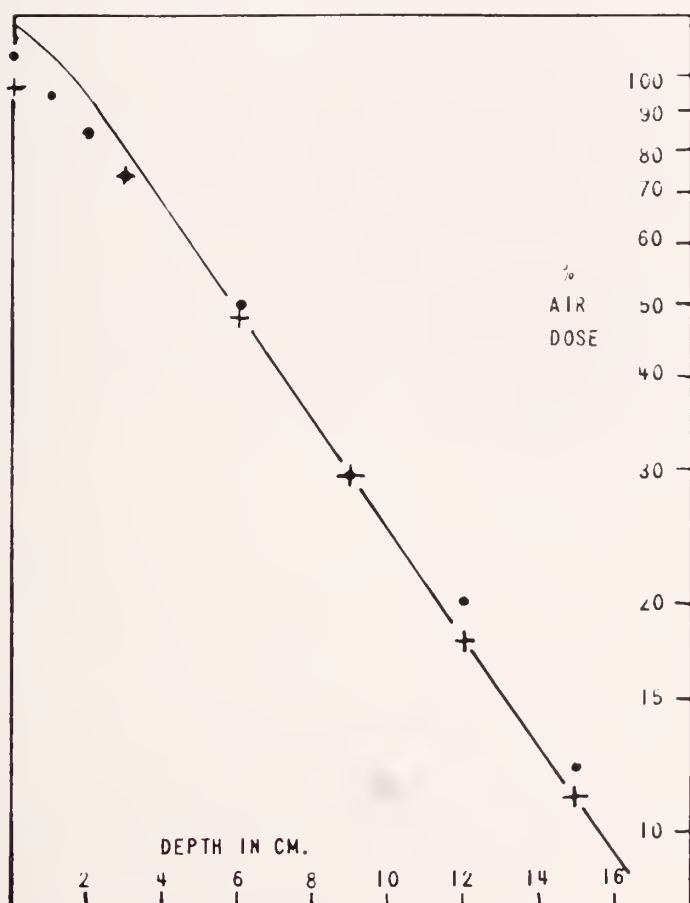


FIG. 3. Depth dose curve for open areas of treatment grids using a 10 x 15 field. The line is the curve of Figure 2 plus the primary curve of Figure 1. The dots and crosses represent measured depth doses behind an open area of the 2-cm. and 1-cm. grids, respectively.

essentially correct and can be used to compute the depth dose for fields of other sizes.

While the depth dose will be a function of HVL, FSD, and treatment area, it will not depend on the size of the grid openings, as long as the openings are much smaller than the treatment area, and are uniformly distributed. If it is desired to know the average dose or to compute an integral dose over the treated volume, it will be necessary to use a suitable weighted average of the doses under an open and a closed area. Such an average is given in the following tabulation of the percent air dose at three depths, for 50 cm. FSD and 1 mm. Cu. HVL, for several different fields.

	5	Depth in cm.	
		10	15
150 cm <sup>2</sup> field (10 x 15).....	93	44	21
60 cm <sup>2</sup> field.....	72	34	17
10 x 15 grid { high.....	57	25	12
{ low.....	23	13	7
40% open { average.....	37	18	9

Roentgrams have been taken with the therapy beam on a patient under treatment, showing the entrance and the exit fields. They verify the existence of a definite grid shadow as deep as 20 cm.

It is not to be assumed that the differences between the high and the low intensities under the grid represent the differences of dosage to the tissues throughout a treatment. Even though the grid is carefully replaced each time at the same position on the skin, the beam direction may vary enough between successive treatments to obliterate partially or totally the distinction between the high and the low dosage regions.

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LIFE'S LATER YEARS  
STUDIES IN THE MEDICAL HISTORY OF OLD AGE

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[New York City]

PART XII\*

THE NINETEENTH CENTURY (CONCLUDED)

As we turn to examine the work of physicians in Great Britain we are once again reminded that information on old age must be sought not only in books and papers with self-explanatory titles but also in widely varied publications devoted to general medicine and surgery. In the course of long years devoted to the study of surgical pathology and to the practice of surgery, Sir James Paget (1814-1899), made many important observations on old age. We note first his study of fatty degeneration of the small bloodvessels of the brain and its relation to apoplexy (74), as well as his study of senile scrofula in which he pointed out that it is too often taken for granted that it is exclusively a disease of the earlier part of life, and that "the same error is in many minds respecting phthisis even though many clear accounts of phthisis in the aged have been written" (75). He had first described different types of aged individuals in his *Lectures on Nutrition, Hypertrophy and Atrophy* (76), characterizing one group in vivid words as the "wiry and tough, clinging to life and letting death have them, as it were, by small installments slowly paid". He returned to this theme in his *Various Risks of Operations* where he pointed out that among the old there are even greater differences than among the young in the ability to recover from operations (77).

"Years, indeed, taken alone are a very fallacious mode of reckoning age; it is not the time, nor the quantity, of a man's past life that we have to reckon; and for this estimate, with a practised eye, looks are less deceptive than a tale of years. . . . They that are fat and bloated, pale with soft textures, flabby, torpid, wheezy, incapable of exercise, looking older than their years, are very bad. They that are fat, florid and plethoric, firm-skinned and with good muscular power, clear-headed and willing to work like younger men, are not indeed good subjects for surgical operations, yet they are scarcely bad. The old people that are thin and dry and tough, clear voiced and bright-eyed, with good stomachs and strong wills, muscular and active, are not bad; they bear all but the largest operations very well. But very few are they, who, looking somewhat like these are feeble and soft-skinned, with little pulses, and appetites, and weak digestive powers; so that they cannot in an emergency, be well nourished".

In his memoirs and letters, edited by his son Stephen, we find references to his own old age that are extremely revealing and moving. In 1894 he gave his last address to students, advising that they should keep science and practice to-

\* This is the second part of the twelfth in a series of articles dealing with the studies in the Medical History of old age. Upon completion of their publication, the installments will be collected and reprinted in the form of a monograph.

gether, and that those who said it could not be done were talking sheer nonsense (78).

Paget was well impressed by the work of Edwin Canton (1817–1885) on the arcus senilis and considered this ocular manifestation the best indication of the tendency to either general or partial fatty degeneration of the tissues (79). Originally published as a series of papers in the *Lancet*, starting in 1850, Canton's studies appeared in book form in 1863. Beginning with a general and microscopic account of the arcus, he also reviewed the literature, quoting among others, Virchow's observation that the eye muscles show marked fatty infiltration in the presence of the arcus. He considered the arcus as of hereditary occurrence and as the result of old age or injury to the eye, noting the occasional absence in advanced age. He described the associated fatty and calcareous degeneration of the costal and laryngeal cartilages, and suggested the influence of intemperance and gout on its development. In all he emphasized that it is an ocular sign of constitutional disorder, a point of view which has only recently been revived by studies on familial and acquired hypercholesterolemia in relation to arteriosclerosis.

In 1853 Henry Bence-Jones (1814–1873) published on diabetes in the aged, citing nine cases, all over 60 years, and differing from Dechambre who had made the statement that sugar was habitually present in the urine of old people (80). Surprised himself at the high incidence of the disease in old people, he stated that it was not universal, that it might occur in the aged without the marked symptoms which usually lead to the detection of the disease. He believed that this modified diabetes might at some time be the cause of the debility ascribed to age alone, and that more frequent urine examinations in the aged would lead to more correct diagnosis and subsequent improvement by use of an animal diet. In connection with this study it is timely to recall that in 1848 Bence-Jones had described the albumose that occurs in the urine of patients with multiple myeloma (81) and that the same year had seen Fehling's quantitative test for sugar in the urine first reported (82).

At this period we note briefly Hodgson's work on the prostate gland (83), Cummins' on the tenacity of life in old age, based on one case (84), and Bailey's uncritical records of longevity, enumerating all persons whose ages had reached 100 years and upwards (85). Garrod's work on gout appeared in 1859, and became the standard work for many years. In it he explained that he himself had never had the disease (86). At the age of 70 years he had his first attack which was accordingly recorded in the second edition. Murchison's classic volume on continued fevers stressed the measurable incidence of typhus, typhoid and relapsing fevers in old age. He described typhus in a man of 84 years (87).

Interest in the pathological anatomy of centenarians is shown in George Rolleston's notes on the postmortem examination of a man supposed to have been 106 years old (88), in Massey's report of the findings in the case of Thomas Geeran, aged 105 years (89), and in Sir G. Duncan Gibb's description of an autopsy of the Tring centenarian (90). These cases supplement those reported in von Mettenheimer's *Sectiones Longaeorum* (58).



The Chelsea Royal Hospital (fig. 7) for invalid soldiers was founded by Charles II and was opened in 1694, occupying a handsome building designed by Sir Christopher Wren and surrounded by extensive grounds including the old Ranelagh Gardens. The hospital accommodated about 500 men, many of whom were advanced in years. Physicians and surgeons attached to the institution have had ample opportunity to study normal and pathological aging. William Cheselden and John Hunter served the old pensioners in their time. Daniel Maclachlan (1807–1870), long an attending physician there, published in 1863, *A Practical Treatise on the Diseases and Infirmities of Advanced Life* (91). In 1932 Martin Lipscomb published his work on old age based on his service at Chelsea (92). More recently, during the Second World War, Dr. Trevor Howell was stationed there and published instructive studies of the old soldiers (93), as well as a description of the famous institution, including its severe punishment during the “Blitz”.



FIG. 7. THE ROYAL HOSPITAL, CHELSEA (FROM FAULKNER)

Maclachlan discussed in his preface the neglect of the problem of the aged, emphasizing the insidious and chronic nature of the diseases, and pointed out that both rich and poor were afflicted. He appreciated “the great industry of French writers, the equal research and recondite reasoning of German authors”, but inclined “more to the practical and sound sense of British and American observers, who in avoiding the trivial distinctions and refinements in description and diagnosis, never lost sight of the great objects of all medical inquiries,—the judicious appreciation of suffering and disease with a view to their amelioration, cure or prevention”. He pointed to the paucity of papers on old age in English literature, but commended Floyer, Carlisle, Day, Halford, Holland, Van Oven and Roget. He expressed his debt to Canstatt, regretting that his great work was never translated by the Sydenham Society, and acknowledged his obligation to Durand-Fardel in recommending that his volume should be in the hands of every practitioner anxious to broaden his knowledge of the diseases of the old. In short, Maclachlan’s work is an accurate reflection of Continental viewpoints with personal observation and common sense.

We note in passing brief contributions such as Fayrer's report of the rapid union of a fracture in a Hindoo aged 96 years (94), Sedgwick's discussion of the influence of age on hereditary disease (95), and Inman's advice on the preservation of health in old age, stressing the bad effects of overwork, and citing the influence of speed in reducing the average duration of life in America by ten years (6). F. E. Anstie discussed nervous affections in old persons expressing great hope for the new remedy, "chloral", and attempting to differentiate minor or constitutional causes for nervousness from real senile dementia (97), Crichton-Browne, one of the pioneer psychiatrists of Great Britain, later emphasized that senile dementia is not a pathological entity, and described three patients ranging from 74 to 86 years to illustrate the distinctions. He believed that the most stupid people are most prone to dementia, that brainwork does not cause brain degeneration, and that the cultivation of science and literature conduce to longevity (98). Woodman described the occurrence of the arcus senilis early in life (99). Annandale cited nine successful operations in aged patients, proving that age alone is no contraindication and that surgery on the old may be undertaken if the patient is in fair health, and the operation likely to prolong life or relieve suffering (100). A basic contribution to the understanding of kidney disease appeared in the classic paper of W. W. Gull and H. G. Sutton on arterio-capillary fibrosis (101). Sir William Gull was noted for his kindly attitude to patients and for his clinical aphorisms among which we find: "The young, the aged and the sick must always be helped" (102). In 1876 the remarkably versatile observer, Jonathan Hutchinson (1828-1913), reported on symmetrical central choroido-retinal disease in senile persons, of which he says, "I have failed to find in our standard works and atlases any description of similar cases. The disease is not improbably a well characterized and important form of senile amaurosis" (103). Ewens recorded operations performed successfully on aged persons, two patients who had the lower lip removed for epithelioma with cheiloplastic restoration, and a tipling female of 87 years who had a finger amputated for epithelioma. He believed that surgery in the aged should be encouraged (104).

From a distinguished scholar and antiquarian came the first application of the scientific method to the study of the records of longevity. William John Thoms (1803-1885), first a clerk in the secretary's office at the Royal Hospital, Chelsea, and later deputy librarian of the House of Lords, had founded the unique periodical, *Notes and Queries*, in 1849. Here for the first twelve or thirteen years after its inception he had inserted without question all the cases of exceptional longevity that were sent to him. Doubt as to the accuracy of these reports were cast by Sir George C. Lewis, in an article on centenarians published by that journal. Thoms' own studies soon convinced him that most of the cases accepted as having lived beyond 100 years were without basis in fact. His *Longevity of Man: Its Facts and Fictions* appeared in 1873 and created such a storm of adverse public opinion as to justify Thoms calling himself "one of the best abused men in England" (105). After discussing the background of popular belief in centenarianism and the views taken by medical men and naturalists of reputation, he laid down rules for the examination of the evidence in each case and then proceeded

to take up the legendary tales of Henry Jenkins, old Parr, and the Countess of Desmond. Of Parr he says, "I really hardly know which is the more to be wondered at—the exceptionally great age of 152 attributed to Parr; or the fact that for upwards of two centuries nobody has appeared to doubt its accuracy, or to have taken the slightest trouble to ascertain upon what evidence it was founded". Most medical writers seem to have accepted Parr's age without question on the authority of Harvey. The appendix to Thoms' book contains Harvey's postmortem on Parr and also the text of the contemporary metrical life, *The Old, Old, Very Old Man*, by John Taylor, the Water Poet.

The evidence and the reasoning brought forward by Thoms was so irrefutable that many persons, scientifically trained and otherwise, reacted violently at the revelation of their own credulity. The controversy found place in the newspapers and medical journals as well as in *Notes and Queries*. Aside from such wordy dis-



"If you would fain know more  
Of him whose photo here is—  
He coined the word Folk Lore,  
And started *Notes & Queries*."

FIG. 8. WILLIAM JOHN THOMS (1803-1885)

pute there were important results from Thoms' iconoclastic views. Most scientists had previously followed Haller's lead and assumed that with sufficient knowledge human life might be prolonged to 200 years. The modern concept of a maximum span of life determined biologically for man as for animals, stems from this disproof of popular wishful thinking. All subsequent work on longevity and on the possibility of extending the life span have depended entirely on Thoms' courageous and completely logical analysis. Later writers, such as Bailey (106) and Young (107) paid well deserved tribute to the pathfinder. Some later authors have misunderstood Thoms' opinion, in stating that he did not believe anyone could live to 100 years. Actually he was interested in getting at the truth, and stated that use of his method not only disclosed the impostor, but supported the case of the truly long-lived. In addition, the attention of the British Medical Association was focussed upon the problem and under the leadership of Sir



George Murray Humphrey (1820–1896) the Association set up a *Collective Investigation of Disease Committee* which addressed itself to *Old Age*, (108) as well as to many other medical problems. In Humphrey's words it constituted "a plan for the collection and utilization of the vast streams of experience which are daily allowed to flow away into the great abyss of waste". The magnitude of the project is evident in its organization which consisted of 54 committees including 800 to 1000 of the leading practitioners.



FIG. 9. SIR GEORGE MURRAY HUMPHREY (1820–1896)

Sir George had been professor of anatomy (1866–1883), and later of surgery (1893–1896) at Cambridge where he had achieved fame as a teacher and a builder of its modern medical school. In 1884 he published remarks on the repair of wounds and fractures in aged persons (109); in 1885, in the annual oration delivered before the Medical Society of London, he discussed *Old Age and Changes Incidental to It* (110); in 1886, described the power of recuperation in old age (111) and in 1889, assisted in preparing the reports of the committee of the British Medical Association (112). In 1889 he brought out *Old Age—the Results of Information received respecting nearly 900 persons who had attained the age of 80*

years including 74 centenarians (113). The general tone of the report is optimistic stressing the importance of longevity, temperance, and the ability of old people to get over operations, injuries and brain affections. This work on old age is significant because it was based on real observation; indeed many of the cases were investigated by Sir George personally. The first chapter is a reprint of Humphrey's oration on the old to the Medical Society of London; the next four are devoted to analysis of the returns on the 74 centenarians as compared with findings of previous investigators. The next four chapters are concerned with men and women between 80 and 100 years, and with the maladies of old age.

This fascinating study of the English population suffers from the defects inherent in the questionnaire method and in the lack of uniformity of the approach of the individual medical examiner. Physicians experienced in the institutional care of the aged to-day are only too familiar with reports sent in by practitioners to the effect that a certain person is suffering only from the infirmities "to be expected with his years", and with the subsequent discovery of diseases ranging from congestive heart failure to senile psychosis. Review of the findings of this collective investigation makes clear that clinical studies of the aged must be correlated with postmortem observation to ensure that important changes may not be totally overlooked.

Of J. Milner Fothergill (1841-1888), who was not related to the famous John Fothergill (1712-1780), one gathers the impression of an able but badly adjusted individual. He engaged in quarrels with his colleagues, and was violent in his expression of opinion, a fact doubtless explained in part by his obesity, diabetes and gout. He had published *The Heart and Its Diseases* in 1872 in London and Philadelphia. The work included a novel chapter on the relation of heart and kidney disease. In 1885 his *Diseases of Sedentary and Advanced Life—a Work for Medical and Lay Readers*, appeared (114). In it we find many interesting opinions, as on the proper use of opium in hopeless malignant disease, the need for sympathetic understanding of the old, and particularly on the impairment of judgment in old age. He considered this "exemplified in self-electing oligarchies of senescent persons, as the Royal College of Physicians for instance—which is little removed from an intellectual mummy swathed in rags and cerate". That he was highly esteemed in the United States is indicated by his holding an honorary M.D. degree from Rush Medical College and his election as Foreign Associate Fellow of the College of Physicians of Philadelphia.

In his address at the opening session of the medical department of the Yorkshire College, Victoria University, Leeds, in 1891, Sir James Crichton-Browne pointed to the reduction of the death rate due to better housing, cleanliness and higher standards of living but drew attention to the fact that this improvement was chiefly in the first half of life (115). He attributed the increase in the death rate in the higher brackets to cancer and to diseases of the heart, nervous system and kidneys, resulting from the strain of modern life, as shown by the fact that women outlive men. He considered old age inevitable only in a sense, and that in spite of changes in the nerve centers with senescence, the freshness of youth may survive. In his opinion the natural span of life is 100 years. He sug-



gested that the promotion of health in old age should be a branch of public health medicine and advocated old age insurance. The speaker was at that time only 51 years of age. Son of the first medical superintendent of the Crichton Royal Institution for mental disorders, he had helped in the establishment of research in neurology and psychiatry and was one of the founders of the periodical, *Brain*. As the Lord Chancellor's Visitor in Lunacy (1875-1922) he acquired wide experience in his specialty. He became a living proof of many of his ideas on longevity and old age, and on his 96th birthday prescribed "no fuss and no fads" as his own formula for a long life. He died in 1938, in his 98th year. He was an ex-

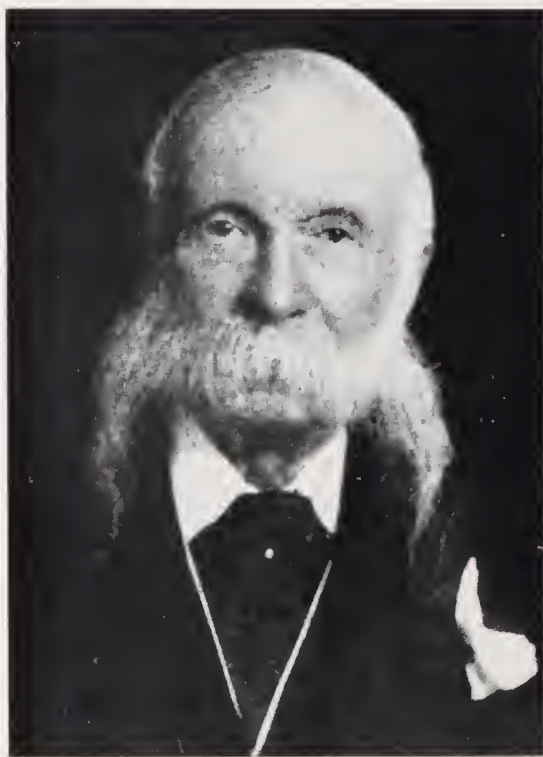


FIG. 10. SIR JAMES CRICHTON-BROWNE (1840-1938)

cellent speaker and wrote well. Especially remembered are his volumes of memoirs. In his *Prevention of Senility* address occurs the memorable dictum: "Old age begins in the cradle and youth still lingers in decrepitude" (116).

George William Balfour (1823-1903) of Edinburgh has been linked with Sir William Tennant Gairdner and Charles Hilton Fagge in London, as making the most important contributions of his generation to the clinical study of the affections of the circulation (117). He had published in 1876 *Clinical Lectures on Diseases of the Heart and Circulation*, and in 1894 his book, *The Senile Heart*, appeared and, according to his biographer, "at once took rank as a classic" (118). This

work reflects the best thinking of its day, both English and European. The nutrition of the myocardium is emphasized, as are also the age changes in the vascular system. As to the role of the coronary arteries, he expressed what was the common error in the reasoning of most physicians for many years, namely, that while coronary sclerosis and angina are frequent concomitants, "coronary sclerosis is too often present where there has never been any angina to permit the circumstances to be looked upon as anything more than accidental". Balfour discussed *angina sine dolore*, first described by Gairdner and considered the senile heart similar to gouty heart of the English and to the *Luxusherz* of the Germans. His therapy was simple, depending chiefly on rest, but using digitalis as a cardiac tonic in the form of *Digitaline Native*, a product that has in recent years again returned to favor.

In closing this section on the English studies of the aged, the reader must be reminded of the steps that had led to the improvement of public health referred to above by Sir James Crichton-Browne. According to Guthrie, credit for having drawn attention to the need for public health legislation belongs to the philosopher, Jeremy Bentham (1748-1832). Thomas Southwood Smith (1788-1861) cooperated with the lawyer, Sir Edwin Chadwick (1800-1890) in efforts to improve sanitation and to eliminate preventable sickness. Sir John Simon (1816-1904) became the first Medical Officer for London, and pushed sanitary reforms of all kinds with great vigor and outstanding success (119). The adoption of an aggressive policy in Great Britain and other civilized countries helped to bring about the profound changes in the age make-up of the population in the next century.

Samuel D. Gross (1805-1884) of Philadelphia was easily the greatest American surgeon of his time. In 1856 he published a *Report on the Causes which impede the progress of American medical literature* (120). He pointed out that the obstructions to the development of a national medical literature were four in number. The identity of the language of the United States with that of Great Britain made it easy for American publishers, in the absence of an international copyright law, to pirate English works and to sell them more cheaply than the originals. Likewise there was a strong disposition in the profession to patronize English rather than American works. Further, the medical press was lacking in independence, failed in its duty to provide constructive criticism, and was too subservient to the publishers of medical books. Lastly the physicians and surgeons of the country had failed to take advantage of the great opportunities offered in the hospitals and in their own practices to make scientific contributions as worthwhile as any emanating from European institutions.

As we proceed to study the work of American physicians in the field of old age we shall see that Gross' strictures are well borne out, with few exceptions. One of these is to be found in the works of the scholarly surgeon himself. Sir George Murray Humphrey writing in 1884 on the repair of wounds and fractures in aged persons (121), quoted from Gross' *System of Surgery* (1859) that age is no barrier to the union of fractures, citing his case of a woman of 100 years in whom union of a fractured humerus took place in the usual time, and that of a woman aged 93 years in whom a fracture of the upper third of the thigh united

in seven weeks. In his treatise on the diseases and injuries of the urinary bladder, the prostate gland, and the urethra he discussed the question of the relationship of prostatic enlargement to old age (122). In his opinion, the fact that this condition occurred in men of advanced age meant that the condition probably originated much earlier, and only showed itself by appropriate symptoms after many years. He quoted Sir Benjamin Brodie's (1783-1862) often repeated remark: "When the hair becomes gray and scanty, when specks of earthy matter begin to be deposited in the tunics of the arteries, and when a white zone is formed at the margin of the cornea, at this same period the prostate gland usually, I might say invariably, becomes increased in size"; and then proceeded to deny the truth.

*"This view, I am inclined to think is more poetical than real. The belief I know is very general, even in the profession, that there is hardly a man of 50 who has not an enlarged prostate. My experience has supplied me with no facts in support of this opinion. The conclusion is too sweeping, the word 'old' is a relative one, and should be used in no other sense in reference to the present subject. Thus, one man is old at 40, another at 50, another at 60, and still another, perhaps, not until he is 70. Gray hair, earthy specks in the coats of the arteries, and a zone around the cornea, are no signs of old age, physiologically and philosophically considered".*

Nichols in his unusually discerning paper on old age stressed the neglect of the aged by physicians, and commended the aged to the attention of philanthropic reformers (123). He reviewed the physical changes and suggested the study of mental hygiene, since unsoundness of mind in the old should not be confused with insanity. Therapeutically he urged caution in the use of mild remedies, and dependence on nature and nursing, lest the patient be further enfeebled. Dutcher's lecture on age was of general character with no reference to actual observations (124). In a paper read before the Cincinnati Academy of Medicine, Dr. S. Gans mentioned the work of Durand-Fardel and of L. "Geis" of Nürnberg, the "latter being the most complete and comprehensive one ever published. I have made that work the principal basis of my report" (125). Geist's name is consistently misspelled throughout the essay which contains no original material.

Lee's study of the arcus senilis was based on 72 cases in negroes, from the Colored Home of New York City, which led him to support Canton's view of its relation to cardiac changes. The author believed that old age is synonymous with fatty degeneration (126). Haskins had previously taken the opposite point of view because he had seen 12 cases of arcus senilis in which there were no symptoms referable to the heart (127). In his opinion the arcus was of but little value to determine the seat and nature of obscure diseases.

Another supercentenarian was reported by "R.D." in the form of "John Gilley, who died in Augusta, Maine, at the age of 124 years". This account followed the familiar pattern including his marriage for the first time between 70 and 80 years to a girl of 18 years, by whom he had eight children. According to his wife, his virility ceased suddenly at 120 years. His only illness was a fracture of the leg. There was no postmortem examination (128).

Smith's and Griscom's essays on the physical indications of longevity were published by an insurance company, bound up with T. S. Lambert's discussion of

longevity with relation to insurance rates (129). S. C. Chew (1808-1863) reported the case of a 97 year old lady with bladder symptoms which yielded to treatment quickly. He considered the case of physiological interest because of the age of the patient, and in view of the absence of signs of disease, wondered what would eventually cause her death. He assumed that it would be fatty degeneration of the heart (130). S. P. Cutler, writing on the physiology and chemistry of old age, stated that with age the cells become clogged with mineralized matter, thereby excluding a portion of the nutritive elements (131). The slow but constant change in hard tissues is proved by the teeth. The organs cool with age unless sustained by alcohol. He suggested limewater as a means of retarding the mineralizing process and the use of foods free of phosphates and a large percentage of vegetable acid. He believed that the scientific study of food might prolong youth indefinitely. Whitaker's study of a case of senile gangrene of both extremities led him only into theorizing (132). Bailey's report of senile prostatic hypertrophy was based on his own cases and reflected the reluctance and inability of surgeons to cope with this condition at that time (133). That the aged were on occasion being studied scientifically rather than theoretically, is shown by one of the rare publications of the famous New York physician, Edward G. Janeway (1841-1911). Discussing the need for postmortem examinations he cited a series of brain cases, many of whom were elderly, in which the diagnosis could only be made by the pathologist (134).

George Miller Beard (1839-1889) was a distinguished neurologist of New York City, who among other contributions is noted for his introduction of the word "neurasthenia" in his work in *American Nervousness with Its Causes and Consequences* (135). In his study of legal responsibility in age (1874) he was interested in the effect of age on the mental faculties, reviewing the work of many famous men (136). He believed that the acuity of the mind declined with age, listing the causes. In his opinion, 70 per cent of the work of the world was done before 45 years, and 90 per cent before 50 years. He cited many authorities who agreed with him and attempted to answer the objections of critics of his idea. These remarks of Beard, interesting in themselves, become more arresting in their reappearance some 30 odd years later in Sir William Osler's famous *Fixed Period* speech which was so horribly distorted by the newspapers. This relationship was apparent to the present writer when he first read Beard's paper several years ago. Only recently Sir James Crichton-Browne's address on the *Prevention of Senility* (116) came to hand in which he stated that Sir William Osler followed "close in the footsteps of the late Dr. George Beard", and in which he dissents vigorously from the viewpoint of both Beard and Osler. Beard's opinions on the decline of mental power with age formed the basis for his discussion of the legal responsibility of old men. This comes up in cases of crimes committed by the aged, in cases of wills that are disputed on the ground of senile incapacity, in fixation of the limit when important officials should be retired and of the age beyond which men should not be eligible to office, and in cases of contested priority in invention and discovery.

He admitted that there are definite exceptions to his rule but stated that great



mental decline and grave cerebral disease are yet consistent with average responsibility. He had no great hope that his views would meet with easy acceptance, since they attacked "principles that are hoary with years, and treasured as heirlooms in the hearts of men; that it seeks to undermine doctrines that are sweeter than life, dear as heaven, and in defence of which many have joyfully gone down to die." He felt that it would be at least fifteen and probably twenty-five years before his theory was generally understood. Actually it has taken more than fifty, for only in the past two decades has modern psychology developed satisfactory methods for measuring accurately the decline of certain mental faculties in relation to age. Beard also wrote the *Longevity of Brain Workers* (137). According to Dana, Beard was very fond of his longevity and work thesis. He believed that brain work was the healthy defense against old age, and that brain workers lived 15 years longer than the average (138).

One of the distinguished practitioners of Louisville, Kentucky, was Lunsford P. Yandell (1805-1878), a pioneer in medical education in the Ohio Valley, an editor of several medical journals and an ardent collector of local fossils. The last paper he wrote was on *Old Age, Its Diseases and Hygiene* (139). The editor of the *American Practitioner* appended a note to the published article that news of the writer's death had just been received as the journal went to press. This is a general paper which indicates clearly the wide range of Yandell's reading and his clear understanding of the problems of older people. His grandson was Yandell Henderson (1874-1944) the well known director of the Yale Laboratory of Applied Psychology, who made such important contributions to our knowledge of the pharmacology and toxicology of gases. In a charming essay, written for the eightieth birthday of his friend, Simon Flexner, Dr. Henderson told of his own boyhood in Louisville, and paid tribute to his grandfather as "dean of the first medical school west of the Allegheny Mountains and a friend of the great McDowell. He was also a geologist of distinction, a writer on medical subjects whose works were highly prized, and a physician who was so much in advance of his time that he gave as small doses of as few drugs as his patients would permit."

The reader will recall that to the translation of the lectures of Charcot by Leigh Hunt, the publisher had added ten additional lectures by Dr. Alfred L. Loomis (1831-1895) of New York City (26). In his introduction to the book Loomis stated that these "embodied, in the main, the salient points in Diseases of Advanced Life which I have been accustomed to impress upon my classes at my clinic in Bellevue Hospital". The topics covered were senile pneumonia, senile chronic catarrh of the bronchi, asthma, atheroma and fatty heart, cerebral hemorrhage and apoplexy, cerebral softening, chronic gastric catarrh, senile constipation and senile hypertrophy of the prostate gland. These topics are discussed in a thoroughly practical manner, emphasizing the differences between the reactions of younger and older patients and devoting considerable attention to treatment. They constitute a good resumé of the medical teachings of that period, and indicate that the leading American physicians were familiar with European interest in older people and with scientific contributions to the subject.



The case report of Frederick Winsor (1829-1889), of Massachusetts bears directly on the history of coronary heart disease. In 1880 he described a case of angina pectoris with cardiac rupture, in which on the basis of the postmortem findings he showed the sequence, coronary occlusion, myocardial infarction and rupture, constituting in the opinion of Benson, Hunter and Manlove, "the first entirely valid presentation of the etiology of cardiac rupture" (140). The patient was an obese merchant of 67 years who had suffered from anginal pain for two and one half years prior to the fatal attack.

In the increasing number of contributions to the topic of old age we note two large groups, general articles and case reports, none of which has the distinction of Winsor's crucial observation. In the first division may be recorded H. Wardner's report on diseases of old people (141), S. W. Caldwell's possible suspension of old age (142), H. C. Wood's hygiene of old age (143), F. C. Clarke's diseases of old age, leaning to Maclachlan (144), R. H. Grube's excellent pathology of old age, based on reports of five national military homes (145), W. J. Rothwell's lobar pneumonia in the aged (146), J. W. Bell's plea for more medical interest in the aged, showing a thorough knowledge of the literature (147), E. B. Montgomery's observations on prophylaxis and treatment (148), I. N. Love's needs and rights of old age, an address delivered at the commencement exercises of the Hospital College of Medicine, Louisville, Kentucky (149), and M. E. Nuckol's old age and the modifications in the course of ordinary diseases when they attack the aged (150).

Among the case reports are F. W. Stuart's case of embolism of the left vertebral artery in a man aged 62 years, with autopsy (151), C. A. Wood's unusual case of epilepsy in a male of 70 years (152), C. W. Hollister's senile gangrene complicated by encapheloid cancer of the face, with spontaneous amputation (153), an exceptional case of tabes in a man of 64 years, reported by N. E. Brill, the first to describe endemic typhus and whom the present writer served as house physician in 1921 at the Mt. Sinai Hospital, New York City (154), F. Heuel's report on the use of moist heat after operations for senile gangrene (155), (155), A. Hanchett's case of senile bronchitis in a female of 90 years (156), Van Harlingen's management of eczema in old people based on 40 personal cases (157), S. D. Lamb's postmortem report of senile hydrocephalus (158), Kammerer's case of sarcoma of the dura mater in a man of 65 years (159), S. M. Bennett's case of alexia in a man of 82 years (160), T. S. K. Morton's study of fractured ribs in the aged (161), and J. H. Emerson's group of aged patients (162).

Cases of senile chorea were recorded by two distinguished Philadelphia practitioners. When Dr. J. M. Anders, in 1889, read his report before the Philadelphia County Medical Society, it was discussed by Dr. William Osler, who said, "Almost all cases of senile chorea are probably associated with organic changes, whereas the evidence is uniformly in favor of the view that the chorea of children is very easily a functional disorder" (163). David Riesman (1867-1940) some years later, described senile chorea in a man aged 75 years and collected 65 additional cases from the literature (164). Pneumonia in the aged was discussed in an excellent paper by James B. Ayer, of Boston, who not only cited his own

cases but also quoted the statistics for different countries, expressing the belief that the frequency of pneumonia in older people is underestimated (165). L. D. White defended a different point of view (166). In his opinion the acute lung disorders in the aged generally termed pneumonia are in reality nearly always instances of pulmonary congestion resulting from a weakened circulation.

In general the surgeons of this period brought more tangible benefits to their older patients. Surgical exploration of the abdomen under aseptic conditions initiated by Billroth and his pupils was carried out in the United States by such men as Gerster, Halsted, McBurney, Fenger, Keen and Kelly. The descriptions of the clinical picture of acute appendicitis by Reginald Heber Fitz, of Boston, in 1886, led to general interest in establishing early diagnosis in such cases. Two worthwhile studies of a common lesion in the aged are L. A. Stimson's (1844-1917) *On doubtful fractures of the neck of the femur and their identity with an alleged form of arthritis deformans* (167) and Nicholas Senn's (1844-1909) treatment of fractures of the neck of the femur by immediate reduction and permanent fixation (168). This paper was based on experimental work with cats. The author's group of eight cases included several of great age. "Patients suffering from this injury are with few exceptions advanced in years and liable to succumb to complications incident to long confinement in bed. The marantic changes in the tissues of the aged and in persons rendered prematurely old by hereditary or acquired causes are known to be antagonistic to a rapid repair, while the anatomical conditions at the site of fracture are well calculated to retard if not prevent production of callus."

The prostate gland continued to challenge surgeons although there were many urologists who still were unwilling to admit that the enlargement of the gland was the only cause of urinary obstruction in older men. Senile weakness of the bladder muscles and a "sclerosis" of the bladder and urethra were considered the primary causes. The papers of Vance (169) and Wilson (170) were general reviews but D. Hays Agnew of Philadelphia urged "prostatotomy" (171). Actually suprapubic prostatectomy developed almost accidentally from operations on the bladder for stone, when it was found that the enlarged middle lobe could be removed without too much difficulty. Pioneers in this operative technique were von Dittel, of Vienna (172), McGill, of Leeds (173), Watson, of Boston (174), and Belfield, of Chicago (175). A. W. Mayo Robson was present at McGill's first operation and became an enthusiastic advocate. His paper is of added interest because the case reports were prepared by the house surgeon, Berkeley Moynihan (176).

At the meeting of the American Association for the Advancement of Science in 1890, Charles Sedgwick Minot (1852-1914), the distinguished anatomist and physiologist of Harvard, addressed the Section of Biology, *On certain phenomena of growing old* (177). This is the first approach to the subject by an American investigator from other than a strictly clinical viewpoint. On the basis of graphs showing the law of biological variations, Minot pointed out the effect of senescence in making the curves asymmetrical. He complained of the lack of vital statistics. He lamented the loss of a large colony of guinea pigs with which

he had worked for five years and which were shaken to death in one night by a bull terrier. In Minot's opinion man's rate of growth diminished from birth to attainment of adult size because of the steady loss of vitality from birth onward.



*Charles Sedgwick Minot*

FIG. 11. CHARLES SEDGWICK MINOT (1852-1914)

The body's power of continuing development steadily decreases. He compared young and adult tissues and found that the most characteristic change with advancing age is the growth in size of the cellular protoplasm in relation to the size

of the nucleus. He believed that this development of the protoplasm is the cause of the loss of the power of growth and forms the physical basis of advancing decrepitude. He later gave to this process the name, "cytomorphosis", and elaborated his views in his book *The Problem of Age, Growth and Death* (178). Here he pointed out the difference in the growth of germ cells and those of adult tissues, which is expressed in the disproportionate bulk of the nucleus and cytoplasm. Death is the inevitable price that the organism must pay for the cytological differentiation on which all higher life depends.

These studies of the first American student of the fundamental cellular changes of senescence conclude our survey of the development of medical knowledge of old age in the nineteenth century. The increasing interest of physicians has gone hand in hand with the rapid growth of the fundamental sciences, with growing understanding of the causes of disease and with improved methods of controlling and treating infectious diseases. The old classical dictum, *senectus ipsa est morbus*, has given way to a concept of a biologically limited life span associated with degenerative tissue changes upon which a variety of disease processes are superimposed. A definite feeling of optimism is gradually pervading the thinking of physicians and surgeons as to the possibility of constructive aid to the aged, and has begun to replace the prevailing attitude of pessimism characteristic of the laity as well as of the profession. We have seen that even before the turn of the century an improved expectation of life was being observed for younger people and that an increase in the incidence of so-called degenerative diseases was anticipated. The actual achievement of unprecedented gains in life expectancy in the first three decades of the twentieth century brought about changes in the age make-up of the population of the civilized world that constituted the greatest challenge that society has ever faced regarding the problems of old age and made it necessary to multiply the methods of coping with them on medical, social and political levels.



## ABSTRACTS

### AUTHORS' ABSTRACTS OF PAPERS PUBLISHED ELSEWHERE BY MEMBERS OF THE MOUNT SINAI HOSPITAL STAFF

Members of the hospital staff and the out patient department of the Mount Sinai Hospital are invited to submit for publication in this column brief abstracts of their articles appearing in other journals.

*Carcinoma of the Gall Bladder.* J. H. GARLOCK AND F. P. SAINBURG. *Surgery*, 23: 201, February, 1948.

The authors report the experience from the Mt. Sinai Hospital in the therapy of carcinoma of the gall bladder over a period of 14 years from 1933 to 1946. During this time 75 patients were admitted to the hospital with the diagnosis of carcinoma of the gall bladder. Of this number 65 were subjected to operation and the diagnosis was confirmed. Of the remaining 10, 5 were moribund on admission and 5 died of unrelated disease. At necropsy all of the latter 10 were found to have carcinoma of the gall bladder. Only 1 patient of the entire group of 65 patients, is alive and well 13½ years after operation. All the remainder died within a period of 35 months after the surgical procedure. The authors go into the question of contributory causes in the production of carcinoma of the gall bladder, and from the evidence at hand, it can be assumed that the only predisposing factor in the production of carcinoma of this organ is evidence of pre-existing gall stones with resulting chronic irritation. On the basis of the findings submitted by the authors in this paper there is justification for the assertion that because the death incidence of malignant transformation in calculus gall bladders far exceeds the prevailing operative mortality of cholecystectomy, it is indicated to remove even asymptomatic calculus gall bladders on these grounds alone.

*Effect of Dibenamine on Blood Pressure in Normotensive and Hypertensive Subjects.* H. HAIMOVICI AND H. E. MEDINETS. *Proc. Soc. Exper. Biol. & Med.*, 67: 163, February, 1948.

Dibenamine hydrochloride, a new sympatholytic and adrenolytic drug was administered intravenously in the dosage of 5 mg/kg of body weight to normotensive and hypertensive subjects. Reduction to normal or below normal levels in resting arterial blood pressure was observed only in benign or moderately advanced essential hypertension, but not in the malignant phase. Orthostatic hypotension occurred in both normotensive and hypertensive subjects. The depressor effect started at the end of the infusion and lasted 24 to 72 hours. All side reactions were transient, and major side reactions occurred only in a few instances. The role of the neurogenic factor in essential hypertension is discussed. The usefulness of dibenamine in evaluating the neurogenic element is suggested.

*Is Anal Fistula a Necessary Sequel to Perianal Abscess?* E. GRANET. *New York State J. Med.*, 48: 63, January, 1948.

In most instances an anal fistula results when a perianal abscess is drained spontaneously or by surgical incision. This sequel can often be prevented if the abscess is afforded early surgical drainage, not only locally, but at the source of infection in the anus. Because of its importance to the problem, the generally accepted concept that perianal suppuration has its source in anal crypts, ducts or intramuscular glands is reviewed in detail. Evidence



that a source of perianal infection can exist in the intramuscular glands or anal ducts without a patent communicating tract to the anus is presented. Inasmuch as a perianal abscess is the precursor of a fistula, it is essential that concurrent with surgical drainage of the abscess, the associated infection in an anal crypt, duct or intramuscular gland be sought for and excised. If this is accomplished, a fistula cannot result. The technique of "stem to stern" drainage in the surgical treatment of perianal abscess is described. This one-stage operation proved feasible and resulted in uncomplicated healing in forty (93 per cent) of 43 patients with infralevator abscesses. This experience demonstrates that anal fistulas probably can be prevented in most instances, if acute perianal abscesses are drained early and completely from "stem to stern."

*Origin of Left Coronary Artery from Pulmonary Artery.* P. E. KAUNITZ. *Am. Heart J.*, 33: 182, February, 1947.

This paper describes 2 examples of the left coronary artery arising from the pulmonary artery, with review of the literature. The ages at death were 3 and 6 months. The right coronary artery was normal in origin and course, and the left arose from behind the left posterior cusp of the pulmonary valve. There was enormous enlargement of the heart due to selective dilatation and hypertrophy of the left ventricle, the endocardium of the left auricle was thickened and opaque, and in the wall of the left ventricle there was degeneration of muscle fibers, persistence of embryonic blood sinusoids, microscopic calcification and intimal thickening of small arteries. These changes are ascribed to anoxia, the left coronary artery distributing pure venous blood at low pressure, and evidence suggests that they occur after birth.

*Experimental Observations on Augmented Unipolar Extremity Leads.* B. KISCH. *Exper. Med. & Surg.*, 6: 1, February, 1948.

In an experimental way it was proven that so-called augmented unipolar limb leads are by no means in accordance with the concept of unipolar electrocardiography. The indifferent electrode against which the aV leads are taken, is not a zero potential, but a potential of considerable height which is different for each investigated limb. Even though some additional information may be received by Wilson's V limb leads or the aV leads, these leads give no information about the real voltage present at the different limbs. Einthoven's standard leads connecting one limb with another limb are, so to speak, 1:1 standard leads, Goldberger's aV limb leads are 1:2 standard leads.

*Endocardial & Endocardial Electrograms & Direct Phonocardiograms in the Calf.* B. KISCH, F. M. GROEDEL AND P. R. BORCHHARDT. *Exper. Med. & Surg.*, 6: 2, May/August, 1948.

Electrograms taken simultaneously from the surface and from the inside of the heart of 5 calves (1-5 days old) were compared with similarly taken cardiograms from man, dog, and rabbit. In the calf there is no significant difference between the electrogram taken over corresponding points of the right and left ventricle. At the base a tall R and a small S are present; at the apex a small R and deep S or a QS. In most of the investigated cases, the electrogram recorded from the inside of the auricle and ventricle shows a high R and small S. In dog, rabbit and man the endocardial electrogram shows a small or absent R and a deep S. Heart sounds were recorded directly from the heart; a second sound could hardly be recorded from the surface of the ventricle, but was very conspicuous in phonocardiograms, obtained directly over the wall of the aorta or pulmonic artery and at the chest wall.

*The Electrogram of the Fish Heart.* B. KISCH. *Exper. Med. & Surg.*, 1: 31, February, 1948.

Electrographic investigations of the heart of fish were done with direct endo- and exocardial leads in fish immobilized by cerebral Procaine anesthesia. The voltage on the surface, even in the small hearts of fish, is quite high. The cardiogram of the auricle as well as that of the ventricle shows a QRS and a T complex, occasionally a U wave. The QRS is of very short duration, the Q-B and the Q-T distances are prolonged. The following abnor-

malities were registered: s-a block, a-v block, extrasystoles, auricular, and ventricular tachycardias and fibrillation. Incomplete contractions of the ventricle and a kind of circus movement can be seen in damaged anoxic hearts. The influence of different drugs on the behavior of the ventricle was tested. Details concerning the anatomy of the heart of selachians are described.

*Laennec Cirrhosis; its Histogenesis with Special Reference to the Role of Angiogenesis.* E. MOSCHOWITZ. Arch. Path., 45: 187, February, 1948.

A study of the histogenesis of Laennec cirrhosis was made from the biologic point of view and with the aid of serial sections. There is every evidence that the earliest stage of Laennec cirrhosis is invariably that represented in a fatty liver. The experimental production of fatty liver and its transformation to cirrhosis may be caused by the interaction of a nutritional deficiency and a deficiency of lipotropic factors. The precise mechanism is not clear. There is evidence that in all cases fatty liver, no matter what its origin, if given sufficient time and the continuance of the factors that produce it, will eventually transform into Laennec cirrhosis. If a proper diet is instituted, the fat eventually becomes more or less depleted, but this does not necessarily prevent the cirrhotic process from continuing, at least for a certain period. Under favorable conditions, the cirrhotic process may cease, and the end result is "latent cirrhosis." The first evidence of beginning cirrhosis is an inflammatory reaction, with round cells, monocytes, plasma cells and a few polymorphonuclear leukocytes infiltrating the periportal spaces. This is the exudative phase. The origin of the cells is discussed. These infiltrations are situated in the periportal spaces between the connective tissue stroma and the adjacent liver cords and there is a special predilection for their occurrence at the angles of the portal spaces where the interlobular vessels arise. They may also be seen similarly placed around some of the hepatic veins. The succeeding phase is a productive one and is represented by a fibroblastic transformation. The third phase is the formation of a capillary network in these areas. The capillaries are produced autochthonously by a conversion of these inflammatory cells through an angioblastic process that is precisely similar to that observed in embryonic angiogenesis. The entire process now resembles a typical aseptic cellular granulation tissue, with fibroblasts, plasma cells, polyblasts, etc. The further development of these capillaries proceeds according to the laws of Thoma. Many of the capillaries collapse, and the resulting cells evolve into progressive fibrosis and ultimate sclerosis. Other capillaries maintain their integrity and, according to the laws of Thoma, lengthen and enlarge and serve as the main blood supply of the granulosus and fibrous strands. Serial section shows that these vessels communicate with the portal veins. No evidence is found of an arterial supply of these strands. Evidence has been submitted that this further evolution is similar to that which occurs in the embryo and in granulation tissue. These granulosus areas at first penetrate into the interlobular septal spaces or into the lobule, and unite with similar adjacent projections from other portal spaces. Often they unite with projections from the hepatic veins, partially converting the blood supply of the liver as in an Eck fistula. These have been termed bi-venous strands. This distribution forms the typical pattern in Laennec cirrhosis and accounts for the eccentricity of the central vein, the periportal distribution of the fibrosis, the distorted lobular pattern and the inclusion of the hepatic veins within the strands of connective tissue. The progressive sclerosis and its elastic transformation convert the liver from a hypertrophic to an atrophic one. In this interpretation the connective tissue structure is the result of the multipotential properties of the cells of the adult mesenchyme, which maintain in a large measure their embryonic potentialities. There is no evidence that the new connective tissue is the direct result of necrosis or of serous hepatitis. Analogous examples of angiogenesis occurring in other tissues have been cited. There is definite morphologic evidence of an intrahepatic collateral circulation. Evidences of regeneration in addition to those previously recognized have been submitted. The newly formed bile canaliculi are not explainable on a unitary basis. There are 3 types. Liver cells have not been seen to proliferate from any of these types. Another evidence of vascular regeneration

is noted in newly formed capillaries with a delicate basement membrane that penetrate the lobule from the periportal strands for considerable distances and terminate in the central vein. These may or may not be accompanied by newly formed bile canaliculi.

*Cerebral Arteriography in Subarachnoid Hemorrhage.* I. S. WECHSLER AND S. W. GROSS. J. A. M. A., 136: 517-521, Feb. 21, 1948.

The authors present their experiences with arteriography in subarachnoid hemorrhage. In 10 cases of subarachnoid hemorrhage in which cerebral arteriography was done with 35 per cent diodrast, 6 patients were found to have vascular malformations and 4 aneurysms of the circle of Willis. The common carotid artery was ligated in 4 patients with vascular malformations and in 4 with aneurysms of the circle of Willis. In 1 of the aneurysm cases intracranial ligation was done in addition. Two patients died following arteriography and common carotid artery ligation. Both were moribund at the time of investigation and arteriography and carotid ligation probably played no part in the fatal outcome. The authors conclude that recurrent attacks of subarachnoid hemorrhage are more likely the result of vascular malformations than ruptured cerebral aneurysms. Arteriography provides a means for accurate diagnosis. It is a relatively safe and simple procedure. Ligation of the common carotid artery in cases of cerebral aneurysms and cerebral vascular malformation is attended with slight risk.

*Whealing Response to Light and Cold with a Note on the Mechanism and the Origin of the Physical Allergies.* H. A. ABRAMSEN. Psychosom. Med., 10: 2, March, 1948.

There are several factors occurring in the whealing syndromes due to light and cold which might lead to certain general considerations regarding the mechanism in these types of physical allergy. 1. The state of the reactivity of the minute vessels of the skin depends upon competing enzyme reactions. These reactions are a series of reaction velocities, the presence and speed of which determine vessel tonus and vessel permeability. 2. These reaction velocities are not fixed and are readily changed, as, for example, in transient dermatographism, where the response to stroking varies with the state of the neurovascular mechanism. 3. The entire surface of the body is usually sensitized in the cases reported here to cold and to light. The abnormal response to cold and to light could have occurred: a. By relatively uniform stimulation of the skin itself with local changes in the skin or minute vessels, b. By a central nervous system mechanism (including a "humoral" and/or "immunologic" process), or, c. By the influence of both factors. 4. All of these dermatologic conditions, apparently, in the early stages may be completely reversible from a pathologic point of view. They are reversible even though the emotional problems have not been resolved. Assuming the reversibility of the lesions, we are justified in stating that the change in reactivity to cold or to light or other factors such as stroke may be an alteration in the usual reaction velocities discussed in 1) (enzymatic), which control the stability of the skin vessels involved. If circumstances arise in which one of the enzyme reactions is interfered with by some emotional stimulus, the tonic state and therefore the reactivity of the blood vessels should change.

*Juvenile Nasopharyngeal Angiofibroma.* H. E. EHRLICH, H. MARTIN AND J. C. ABELS. Ann. Surg., 127: 513, March, 1948.

This rare, highly vascular, essentially benign neoplasm, encountered in 29 patients from 1927 to 1946, occurs in pubescent males and usually regresses spontaneously when full sexual maturity has been reached. Evidence is presented to support a sex-endocrine relationship. There were no instances of malignant transformation; the authors believe that those cases previously reported by others as malignant were not critically selected. The usual symptoms are nasal obstruction, recurrent epistaxis, facial deformity, and unilateral exophthalmos. Paranasal sinus and ear infections are frequent complications. The presence, in pubescent or adolescent males, of a bulky vascular nasopharyngeal mass that has grown forward to block one or both choana and is associated with these symptoms should suggest

the diagnosis, and biopsy taken for histologic confirmation. Treatment comprises relief of symptoms and arrest of the growth, during the period of activity, since complete eradication, either by surgery or irradiation, is impossible and attempts thereat are hazardous. A systematic plan of treatment is outlined: hormone therapy (testosterone propionate), ligation of the external carotid arteries, x-ray and radium therapy. Surgical removal of the bulk of the tumor through a transmaxillary approach is described but recommended only in patients with marked facial deformity or with symptoms that cannot be controlled by more conservative methods of treatment. The prognosis is excellent if the case is properly managed. The greatest hazard to life and permanent disability lies in injudicious treatment.

*Gangrene of the Extremities of Venous Origin.* H. HAIMOVICI AND G. SUFFNESS. *Am. J. M. Sc.*, 215: 278, March, 1948.

A case of gangrene of the lower extremity due to venous occlusion is reported. The clinico-pathologic characteristics of this type of gangrene, namely, extensive thrombosis involving all the veins and patency of the arterial system, are described. Pertinent therapeutic indications are stressed.

*The pH of Gastric Mucous Secretion After Equilibration In Vitro with Alveolar Air.* F. HOLLANDER AND F. U. LAUBER. *Federation Proc.*, 7: 1, March, 1948.

It was previously found that gastric mucous secretion can possess pH's as high as 9.2. These observations obtain for secretion as it occurs inside the gastric cavity, but such "alkaline" material probably has undergone CO<sub>2</sub>-loss between secretion and collection from the pouch. Therefore, specimens collected in response to eugenol and mustard oil were equilibrated with human "alveolar" air, and pH's determined. Blood plasma was studied similarly. After such equilibration, the pH of gastric mucous was constant, and approximately that of blood plasma. This suggests that the pH of mucous inside the gastric cell and at the instant of ejection into the gastric lumen is approximately that of venous blood.

*The pH of Gastric Mucous Secretion.* F. HOLLANDER, U. LAUBER AND J. J. STEIN. *Am. J. Physiol.*, 152: 645, March, 1948.

Electrometric pH's were determined for 579 specimens of gastric mucous secretion collected from dogs' Heidenhain pouches. For this purpose, 12 topical stimuli were employed. The range of these pH values was 4.00 to 9.22, with a mean of 7.65 and a standard deviation of 1.08. The data were broken down into pH sub-ranges, and also according to stimulus. Analyses of the data support the conclusion previously reached by the authors that clove oil and eugenol, with mean pH's above 8.0, are considerably more effective mucous stimuli than any other mucigogues in the series. These results indicate that, in the intact anaesthetized stomach, pH's of 8 to 9 may easily occur in response to even mild mucigogue action.

*The Sigmoid as a Source of Right Sided Symptoms.* A. S. LYONS. *Ann. Surg.*, 127: 398, March, 1948.

Carcinoma and diverticulitis of the sigmoid are sources of *right-sided* abdominal symptoms and signs more commonly than is generally realized, and may be confused with acute appendicitis. Eighteen cases are reported to illustrate the probable mechanisms of production of right sided symptomatology by sigmoidal lesions: 1—Position of the sigmoid to the left of the midline because of mobility or anatomical course; 2—Perforation of sigmoid with spillage of contents into right iliac fossa; 3—extension of perisigmoidal abscess toward the right; 4—Adherence of right sided structures to the sigmoidal lesion; 5—excessive cecal distention; 6—Situs inversus.

*Mixed Infection in Subacute Bacterial Endocarditis; Report of Two Cases.* M. G. OLINGER. *Arch. Int. Med.*, 81: 334, March, 1948.

Two cases of subacute bacterial endocarditis with mixed infection which responded favorably to antibiotic therapy are reported. In the first case *Corynebacterium pseudo-*



diphthericum (hoffmannii) and *Streptococcus viridans* were present, the former being sensitive to 0.1 unit and the latter to 0.02 unit of penicillin per cubic centimeter. When the corynebacterium was recognized as one of the infecting agents, penicillin was given in adequate dosage. In the second case *Streptococcus viridans* and *Hemophilus parainfluenzae* were found. The former organism was susceptible to 0.2 unit of penicillin and to 8.0 units of streptomycin per cc. The latter organism was susceptible to 2.5 units of penicillin and to 0.8 unit of streptomycin per cc. Large doses of both antibiotics were essential in this case, the patient receiving 2,400,000 Oxford units of penicillin daily for 8 weeks and 4 grams of streptomycin daily for 10 days. It is suggested that mixed infection in endocarditis may be more frequent than has been commonly recognized.

*A Biological Method for Determination of Curare and Erythroidine Alkaloids.* E. P. PICK AND G. V. RICHARDS. *Proc. Soc. Exper. Biol. & Med.*, 67: 329, March, 1948.

A biological method for qualitative and quantitative determination of curare and erythroidine is described. The method depends upon the antagonistic action of these alkaloids on the excitement and tail phenomenon in morphine-poisoned mice. The median effective dose and standard error for crystalline *d*-tubocurarine chloride is  $2.8 \pm 0.2 \mu\text{g}$ ; for Strychnos Curare (Merek),  $24.0 \pm 2.0 \mu\text{g}$ ; for dihydro- $\beta$ -erythroidine bromide,  $44.0 \pm 3.0 \mu\text{g}$ ; and for Intocostin (Squibb),  $20.0 \pm 2.0$  milliumits. Far higher doses of other drugs, including quaternary alkaloids, are necessary to antagonize the effect of small amounts of morphine in mice.

*Bleeding of Vesical Origin in the Menopause Confused with Uterine and Rectal Bleeding.*

I. C. RUBIN. *Urol. & Cutan. Rev.*, 52: 3, March, 1948.

Vaginal bleeding in the menopause, unless promptly identified as of genital origin, should cause suspicion of possible vesical or rectal pathology. Two cases of vesical carcinoma are cited in which the bleeding though of long standing was not identified by the patient as issuing from the urethra. In both cases a dilatation and curettage were done mistaking the source of the bleeding. To avoid confusion, a diagnostic routine has been outlined to trace the bleeding to its true source.

*Serological and Biological Characteristics and Penicillin Resistance of Nonhemolytic Streptococci Isolated from Subacute Bacterial Endocarditis.* S. S. SCHNEIERSON. *J. Bact.*, 55: 393, March, 1948.

The serological and biological characteristics and the in vitro penicillin resistance of 34 strains of nonhemolytic streptococci isolated from 32 cases of subacute bacterial endocarditis were investigated. The existence of a new variety of nonhemolytic streptococcus based upon serological and biological characteristics and designated as *Streptococcus s.b.e.* was confirmed. 9 of the strains were in this group, 2 were *Streptococcus salivarius*, 2 enterococci and the remaining 21 were considered to be in the heterogeneous group, unclassified streptococci. The resistance of the *Streptococcus s.b.e.* group to penicillin was found to be slightly higher than the unclassified streptococci isolated from this disease, but none of the strains were markedly resistance to the antibiotic in vitro. The streptococci of the enterococcus group were found to be markedly resistant to penicillin.

*Antibacterial Properties of 4-Amino-2-Methyl-L-Naphthol Hydrochloride.* G. SCHWARTZMAN. *Proc. Soc. Exper. Biol. & Med.*, 67: 376, March, 1948.

4-Amino-1-methyl-1-naphthol hydrochloride (water soluble vitamin K) possesses marked antibacterial activity against gram positive and gram negative organisms. The compound is strongly effective against gram positive organisms in presence of broth, casein hydrolysate and blood serum, and against gram negative organisms in synthetic medium. The activity against the latter organisms is antagonized in broth medium. Casein hydrolysate and mouse and rabbit sera antagonize the antibacterial activity of Synkamin against *E. coli* in a significantly lesser degree than broth, namely, in dry weight ratios of 125:1, 65:1,



50:1, respectively. The presence of an amino substituent group and partial oxidation of the substance under carefully controlled conditions play an important role in the antibacterial activity described.

*Mid-Leg Amputations for Gangrene in the Diabetic.* S. SILBERT. *Ann. Surg.*, 127: 503, March, 1948.

Contributing to the present unsatisfactory picture of diabetes is the high mortality which results from thigh amputations for gangrene. Since the technical procedure of a thigh amputation is simple and requires no great skill, the prevailing high mortality indicates that this procedure is too severe for the average patient with diabetes. Amputations can be performed safely below the knee in diabetic patients, even when the popliteal artery is closed and oscillometric readings indicate a seriously deficient circulation. Every death which occurred before the stump was healed was regarded as an operative mortality, even though the cause of death was entirely unrelated to the surgical procedure. In the entire group of 127 diabetic patients there were twelve deaths, a mortality of 9.4 per cent. Only about 40 per cent of diabetic patients will survive longer than three years after amputation of a leg. Of those who survive, about 40 per cent will require amputation of the second leg.

*Orthodontic Therapy as Limited by Ontogenetic Growth and the Basal Arches.* J. A. SALZMANN. *Am. J. Orthodontics*, 34: 4: 297, April, 1948.

The stress produced by muscle or by orthodontic appliances exerting pressure on the teeth will not change the basic architecture of the jawbones as long as these forces are not strong enough to overcome the resultant stress which the jaws are able to withstand. Facial appearance is influenced by the soft tissues as well as by the relationship of the underlying bones and the occlusion and axial position of the teeth. The movement of a tooth or a number of teeth by orthodontic means, or otherwise, into a different occlusal relationship, whether normal or abnormal, will not change the form of the basal arch, which is an intrinsic part of the over-all morphology of the jawbone, even when the alveolar process itself which follows the teeth is changed as a result of orthodontic tooth movement. Orthodontic tooth movement which brings the teeth into conflict with the intrinsic lines of stress of the jaws, as evidenced by the relationship of the teeth to the basal arch and their angular relation to the base of the mandible, results in collapse.

*The Effect of Physically Induced Pyrexia on Gastric Acidity.* J. BANDES, F. HOLLANDER AND W. BIERMAN. *Gastroenterology*, 10: 697, April, 1948.

The inhibitory effect of fever on gastric acid secretion was studied in 16 experiments (9 subjects) using diathermy and radiant heat in a fever cabinet. Pyrexia of 102-106°F. was induced and maintained for  $3\frac{1}{2}$ -5 $\frac{1}{2}$  hours. Anacidity developed in only 8 of the tests. The failure of anacidity production in the others is ascribed to lesser degree and duration of fever. Normal gastric analysis curves were obtained within 24 hours after treatment in 4 of the above anacidity patients. The other anacid patients, unable to be followed up in 24 hours, showed recovery within 2 weeks. Because of the fleeting character of the anacidity, physically induced pyrexia offers no promise in ulcer therapy.

*Cerebral Arteriography.* S. W. GROSS. *Surgical Clinics of North America*. New York Number, 405, April, 1948.

The author reviews the history of cerebral arteriography and describes the technic for direct cerebral arteriography with 35 per cent diodrast. The normal arteriogram is described. Arteriography with diodrast is indicated for the detection and localization of intracranial aneurysms, vascular malformations, arteriovenous fistulas and vascular tumors. Cerebral arteriography is also useful for the localization of brain tumors when the results of air studies are not conclusive.

*Hyaline Membrane of the Iris.* J. LAVAL. Am. J. Ophth., 31: 461, April, 1948.

In eyes with longstanding glaucoma, it is not uncommon to find a hyaline membrane lying on the anterior surface of the iris. This membrane is continuous with Descemet's membrane of the cornea and occludes the filtration angle. In this way the glaucoma is aggravated. A case report is given together with micro-photographs of the sectioned eye.

*Vogt-Koyanagi Syndrome.* J. LAVAL. Arch. Dermat. & Syph., 57: 235, February, 1948.

Vogt-Koyanagi Syndrome is described and the bibliography is reviewed. The final conclusion is arrived at that the disease is due to a virus infection. A case is presented with the typical uveitis, retinal detachment, poliosis, alopecia and dysacusia. This patient had an extremely stormy course with secondary glaucoma necessitating operative interference. The end result of 20/30 vision in one eye was considered extremely good. Later the hair grew back without any greyness of the hairs, and hearing returned to normal.

*X-Ray Therapy for Orbital Neoplasm.* J. LAVAL. Eye, Ear, Nose & Throat Monthly, 27: 363, August, 1948.

A case is reported of a young girl who had an incomplete removal of a fibro-sarcoma of the left orbit at the age of 13 years. Deep X-ray therapy was used resulting in complete cure, but with cosmetic damage to the left eyeball. However, the cosmetic defect was much less than an extenteration would have been. The follow-up period was more than 13 years. It is advocated that even though the pathologist and the X-ray therapist may consider the neoplasm as not being radiosensitive, it is still advisable to administer radiotherapy with at times very good results.

*Apical Systolic Murmur.* A. M. MASTER. Arch. Int. Med., 81: 518, April, 1948.

Experience during the recent war brought into prominence the consequences of failure to recognize apical systolic murmur as an indication of organic disease of the mitral valve. Army and Navy personnel with such murmurs had to be reexamined frequently, lost valuable time in hospitals, were a burden to the government and a source of additional expense. Finally, in certain instances, heart failure developed under the mental and physical exigencies of war. For adequate protection of patients, loud systolic murmurs at the apex unaccompanied with a systolic thrill, an enlarged heart, diastolic murmur, an abnormal electrocardiogram and evidence of heart failure should be most carefully appraised. The diagnostic signs to be sought in physical examination are a loud first apical and a loud second pulmonic sound. A prolonged murmur is significant. A "musical," "sea-gull," "harsh" or "constant" murmur tends to confirm the presence of organic heart disease. Patients should be examined repeatedly, in different positions and after exercise, since the murmurs of early valvular heart disease are transient.

*Action of Curare Alkaloids on Erythrine Alkaloids on Morphinized Mice.* E. P. PICK AND G. V. RICHARDS. Arch. Internat. de pharmacodyn. et de therap. 76: 183, April, 1948.

1) Restlessness and erection of the tail induced in mice by subcutaneous injection of morphine sulfate (0.5 - 1 mg.) are abolished within 5-10 minutes after subcutaneous or intraperitoneal injection of very small amounts of curare or erythroidine without alteration of the peripheral receptive nerve-muscle apparatus. Minimal effective doses are: Crystalline d-tubocurarine chloride, 5 micrograms, Intocostrin, 20-25 milliunits, strychnoscurare, 30 micrograms, and crystallin dihydro-B-erythroidine bromide, 50 micrograms. Other curare-like alkaloids such as quinine methochloride, tetramethylammonium chloride, or tetraethyl ammonium chloride are effective only in much higher doses. Quinine sulfate, quinine-ethochloride, thiamine chloride, acetylcholine-chloride, guanidine chloride, histamine hydrochloride, nicotine base, and scopolamine bromide are either ineffective or only very slightly effective. Bulbocapnine checks the restlessness of mice, but not the tail rigidity. 2) Crystalline d-tubocurarine hydrochloride and dihydro-erythroidine

bromide in doses of 5 micrograms, and 50-60 micrograms respectively (amounts sufficient to abolish evidence of morphine excitement in mice) are ineffective in antagonizing strychnine, picrotoxin or metrazol convulsions. 3) Amounts of prostigmine methylsulfate which are entirely without outward effects in morphinized mice inhibit the action of small doses of curare on the excitement and spinal reflex of morphinized mice. The same innocuous amount of prostigmine will to a large extent protect similarly prepared animals against the fatal effects of large doses of curare. Evidence of morphine poisoning in these animals is largely eliminated. 4) Crystalline d-tubocurarine chloride and dihydro-B-erythroidine bromide are quickly destroyed in the living mouse. Five micrograms of d-tubocurarine chloride are inactivated after subcutaneous injection within 100 minutes; after intraperitoneal injection, within 30 minutes. Fifty micrograms of dihydro-B-erythroidine bromide are destroyed within 30 minutes. 5) The inactivation of curare may be partly effected by the liver since d-tubocurarine chloride incubated with homogenized mouse liver loses 65-80 per cent of its activity within 2 hours. 6) It is suggested that the depressant effect of curare alkaloids on the morphine excitement in mice is produced by a direct action on the brain or spinal cord and should therefore be distinguished from the peripheral curare action on the motor end plates.

*Atresia of the Tricuspid Valve with Transposition of the Great Vessels.* A. ROBINSON, J. E. HOWARD. *Am. J. Dis. Child.*, 45: 575, April, 1948.

Report of a case of atresia of the tricuspid valve with transposition of the great vessels in a 6 months old male. On admission he was dyspneic and mildly cyanotic, although previously he had only occasionally "breathed heavily". X-ray showed pneumonia of the right upper lobe and cardiac enlargement. Despite improvement in the infection the patient eventually succumbed to heart failure following blood transfusions. Post-mortem findings are given. The importance of the ECG and x-ray in making a correct ante-mortem diagnosis is discussed. Of particular significance is the presence of left axis deviation and abnormal P-waves in a cyanotic infant.

*Chorda Tympani Nerve Graft. A Preliminary Report of a New Technic Used in Surgical Fenestration of the Labyrinth.* S. ROSEN. *Arch. Otolaryng.*, 47: 428, April, 1948.

Since the beginning of fenestration surgery the greatest difficulty has been closure of the fenestra and postoperative labyrinthitis. Many kinds of material were used to cover the fenestra including, fat, conjunctiva, muscle, peritoneum, fascia, cartilage, platinum and other substances. These were used to protect the underlying membranous labyrinth and inhibit osteogenesis. All of these have failed of their objective. The author instituted the first living tissue to cover the fenestra in fenestration history; a pedicle graft of the chorda tympani nerve which is evulsed from its attachment to the facial nerve. In a series of 8 consecutive cases operated upon with the chorda tympani nerve graft technique useful hearing was achieved within 2 weeks of operation and continued improvement during the first 7 months. These results are approximately 15 to 20 decibels better than those reported by others.

*The Surgical Treatment of Chronic Anal Fissure.* R. TURELL. *Surg., Gynec., & Obst.* 86: 434, April, 1948.

The author believes that the treatment of chronic anal fissure or ulcer is always surgical. In this paper a rational operative procedure as carried out in 270 patients is described and illustrated. The operation comprises wide excision of the ulcer-bearing area, the extirpation of the involved anal crypt or crypts with the sentinel pile and polyps, and the performance of a posterior sphincterotomy. The author's modified posterior sphincterotomy consists in the excision of a small portion of the subcutaneous component of the external anal sphincter muscle. This is done in order to prevent early reapposition of this muscle and to insure ample drainage which in turn promotes better restitution of the inflamed anorectal tissues. The preoperative and postoperative management is described in detail.

## BOOK REVIEWS

*Diseases of the Heart*, by FRIEDBERG, CHARLES K.: Philadelphia, Pa., W. B. Saunders & Co., Price \$11.50, pp. 1081.

Many new volumes on cardiovascular disease have appeared in this country and abroad in recent years due to rapid advances in knowledge of the pathologic physiology of circulatory disorders. Some are merely compendiums of current clinical practice; others deal with fragments of the subject such as coronary artery thrombosis, arterial hypertension, congenital heart disease, or electrocardiography. This volume by Dr. Charles K. Friedberg encompasses the entire field of cardiac disease so completely and in so up-to-date a manner that it can serve either as a textbook for advanced students in internal medicine and cardiology or as an excellent work of reference. The subject matter is presented with new emphasis upon underlying physiological disturbances affecting cardiac output, blood volume, extracellular fluids, peripheral and intracardiac pressures and oxygen concentrations, body fluid and tissue electrolytes, peripheral, renal, and pulmonary blood flow. The scientific and clinical literature is well covered.

Although the text deals extensively with the newer knowledge of cardiovascular physiology, this is employed as a means to interpret and improve current methods of clinical diagnosis and therapy of the diseases of the heart. Because of its new approach to the subject, its thoroughness, and its concise style, this book is one of the best of its kind. It deserves to be in the library of all students and practitioners as well as teachers of medicine.

GEORGE BAEHR, M.D.

*Coronary Artery Disease*, by ERNEST P. BOAS, M.D. AND NORMAN F. BOAS, M.D. Chicago: The Year Book Publishers, 1949. 399 pp. Price \$6.00.

This monograph, presented by the publishers as one of their General Practice Manuals, is one of the best expositions of the subject. It is clearly printed on excellent paper and is richly illustrated with pathological sections, roentgenograms and numerous electrocardiograms which are well chosen. Although the CF precordial leads depicted in this book are now being replaced by V leads, their use does not significantly impair the value of the illustrations. There are some 400 well-distributed references, set at the bottom of the page. The references are up-to-date, including some in 1948.

About one quarter of the text is devoted to the anatomy, embryology, physiology, pathology and pharmacology of the coronary arteries and coronary circulation. The authors discuss the etiological factors, associated diseases and prognosis of clinical coronary arteriosclerosis under the heading of "The patient with coronary sclerosis." The occurrence of electrocardiographic evidence of myocardial damage without abnormal physical signs or symptoms is presented under the heading of "silent coronary artery sclerosis." Angina pectoris and precordial pain not caused by coronary disease are clearly differentiated in distinct chapters. Coronary insufficiency is also discussed in an individual chapter but the authors refer to it as "a classification of convenience, not, as some would have it, a clinical entity." The discussion of treatment is detailed and includes the general management of the patient, individual medications, surgical management and the treatment of cardiac irregularities and of the late effects of coronary disease. The nonarteriosclerotic diseases of the coronary arteries are carefully classified and briefly but adequately considered. There is also a chapter on the patient with coronary artery disease in industry devoted to subjects such as employability, workman's compensation and the relation of trauma and strain.

The outstanding merit of this monograph is its sound and practical presentation of the clinical aspects of coronary artery disease based on the actual observation and management of thousands of patients with this disease. In general, theoretical and controversial subjects are omitted or briefly discussed or only the authors' viewpoint mentioned. However, the dogmatism which occasionally results enhances rather than detracts from the value of the book for the physicians to whom it is primarily directed.

The book is unequivocally recommended to all physicians who are apt to encounter clinical problems in coronary artery disease.

CHARLES K. FRIEDBERG, M.D.



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## CONTENTS

	PAGE
PHYSIOLOGY OF CHOLESTEROL METABOLISM IN MAN. <i>S. J. Thannhauser, M.D., Ph.D.</i> .....	79
AN ULTRAVIOLET SPECTROPHOTOMETRIC METHOD FOR THE DETERMINATION OF $\Delta^3,^5$ ANDROSTADIENONE-17 IN THE URINE. <i>Louis J. Soffer, M.D., Jacob Chanley, Ph.D., Mildred D. Jacobs, A.B., and H. Peter Laqueur, M.D.</i> .....	98
THE ROLE OF ANTIBODIES IN INSULIN RESISTANCE. REPORT OF A CASE. <i>Robert M. Berne, M.D. and Robert S. Wallerstein, M.D.</i> .....	102
HODGKIN'S DISEASE LOCALIZED TO THE ANTERIOR MEDIASTINUM: CLINICAL, ROENTGEN AND SURGICAL CONSIDERATIONS. <i>Emanuel Salzman, M.D.</i> .....	112
HEMANGIOMA OF THE PONS. CASE REPORT AND REVIEW OF THE LITERATURE. <i>Philip S. Bergman, M.D.</i> .....	119
INSPIRATORY INCREASE OF THE PULSE AMPLITUDE, ITS RELATION TO PULSUS PARADOXUS. <i>Marvin C. Becker, M.D., Donald S. Kent, M.D. and Irving G. Kroop, M.D.</i> .....	132
RESTORED VIABILITY OF IMPLANTED PRESERVED NECROCARTILAGE IN RHINOPLASTY. <i>Irving Goldman, M.D.</i> .....	142
ABSTRACTS.....	145



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## XANTHOMATOSES\* \*\*

S. J. THANNHAUSER, M.D., Ph.D.†

*Boston, Mass.*

## PHYSIOLOGY OF CHOLESTEROL METABOLISM IN MAN

**SYNTHESIS OF CHOLESTEROL.** Cholesterol is supplied for the organism by food (exogenous quota) and by synthesis in the organs (endogenous quota). The synthesis occurs in all organs but especially in the liver. The reticulum cells and histiocytes probably maintain the functional possibilities of embryonal fat cells for the synthesis of all kinds of lipids.

Our early experiments show that the material for synthesis of cholesterol is derived from all food stuffs and is not solely provided by the metabolites of fat. Smedly-McLean was the first to demonstrate that yeast cells synthesize 50 per cent of unsaponifiable matter, *i.e.*, cholesterol from Deuterium-labeled acetic acid. Schoenheimer feeding Deuterium-labeled substances of low carbon chains found Deuterium-containing cholesterol in these animals. Bloch finally demonstrated that Deuterium-labeled acetic acid incubated with liver slices produced Deuterium-labeled cholesterol.

Low carbon chain metabolites like acetic acid may not only derive from fat but also from carbohydrate and protein metabolism. It is evident, therefore, that synthesis of cholesterol can not be prevented by restriction of any kind of food. For this reason, a diet free of animal cholesterol can only reduce the cholesterol content of the serum to a certain degree but can never result in a definite reduction of the cholesterol content of the tissue fluids.

**DESTRUCTION OF CHOLESTEROL.** Up to the present, no enzyme of the intermediary metabolism of animals has been found which is capable of splitting the sterol skeleton. Balance experiments, however, carried out on whole animals, as well as feeding experiments in man, show that fed cholesterol is only partly recovered by digitonin precipitation or the Liebermann-Burchard reaction. Schoenheimer demonstrated in a balance experiment of 7 weeks duration on a xanthomatous patient that 20 gm. cholesterol could not be accounted for. Negative balances were interpreted as significant for a destruction of the sterol skeleton in the intermediary metabolism. Such a claim can not be maintained since an enzyme capable of splitting the sterol skeleton is not found in the animal organism. Ottenstein, as well as Beumer, however, demonstrated that bacteria of the intestines can accomplish what the intermediary metabolism can not achieve,

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namely, cholesterol disintegration. The same ability of fission of the sterol skeleton was shown for bacteria of the soil by Tuarfitt as well as by Tak. It may be concluded that the cholesterol deficit in balance experiments is due to bacterial cholesterol disintegration of the intestines rather than to its degradation in the intermediary metabolism. It seems a biological peculiarity that the animal organism, in contrast to bacteria, can synthesize organic ring systems like purins, pyrrols and sterols, but is not capable of splitting these ring structures by enzymatic reactions.

The changes which may occur in the cholesterol molecule in the intermediary metabolism are but few and limited to the side chains such as esterification, hydrogenation, formation of dihydrocholesterol. The sterol hormones apparently are synthesized in the endocrine organs where they originate and are not metabolically formed from cholesterol. The metabolic changes occurring in the sterol hormones also involve only their side chains. For example, the hydroxyl groups of pregnanediol are oxidized to ketones, thus forming progesterone.

**ABSORPTION OF CHOLESTEROL.** The presence of neutral fat in the intestines facilitates the absorption of cholesterol. They are mainly absorbed as cholesterol esters. Man absorbs only, or at least mainly, cholesterol of animal origin. Schoenheimer and his co-workers demonstrated that vegetable sterols are not absorbed in humans. This selective absorption of cholesterol and its esters is unexplained. Not even dihydrocholesterol is absorbed. Herbivorous animals absorb vegetable and animal cholesterol but they can not excrete animal sterols. In herbivorous animals, animal cholesterol is retained. Hypercholesteremia and deposition of cholesterol in the arteries and tissues results. Herbivorous animals, therefore, should not be used for comparative experiments of cholesterol metabolism.

**EXCRETION OF CHOLESTEROL.** Cholesterol is excreted with the bile and directly in the intestines. The concentration of cholesterol in the bile fluid is much lower than that in the serum. Cholesterol, as well as its bacterial degradation products, is partly reabsorbed from the intestines. The reabsorption of bacterial degradation products from the intestines may lead to a misinterpretation of experiments which are carried out for the purpose of proving a conversion of cholesterol into bile acids in the intermediary metabolism. Bloch and Rittenberg injected Deuterium-labeled cholesterol intravenously in dogs. The common bile duct of such a dog was anastomosed with the renal artery before the injection. Small amounts of Deuterium-labeled bile acids were recovered in the urine of these animals. This result was considered as a proof of the conversion of cholesterol into bile acids in the intermediary metabolism. However, one can not exclude the possibility that in such an experiment Deuterium-containing cholesterol was also directly excreted in the intestines and split by bacteria of the intestines and reabsorbed as Deuterium-containing small molecular split products. The reabsorbed Deuterium-containing material may have been used for the synthesis of bile acids in the liver. The bile acids which have a different steric configuration from cholesterol are synthesized in the liver independently of the cholesterol supplied by the blood as our experiments have demonstrated. The daily produc-

tion of bile acids is as high as 2 to 3 gr., a figure which can not be explained otherwise except by their synthesis in the liver independent from cholesterol supply by the blood stream.

Three different possibilities have to be considered for the explanation of an accumulation of cholesterol in the serum, cells and tissues.

(1) Cholesterol *infiltration* into the cells has as a prerequisite, cholesterol accumulation in the serum, *i.e.*, hypercholesteremia. Hypercholesteremia, on the other hand, may originate from two entirely different processes. (a) Hypercholesteremia may be caused by an imbalance of cholesterol synthesis and cholesterol excretion. Example, "essential familial hypercholesteremic xanthomatosis." (b) Hypercholesteremia may be associated with an increase of neutral fat in the serum. Example, "idiopathic and secondary hyperlipemia with eruptive xanthomata."

(2) Increased cholesterol *synthesis* within certain cells resulting in an accumulation of cholesterol within the cell. Such a process does not require an increased supply of cholesterol from the serum. The blood cholesterol is normal. Example, "eosinophilic xanthomatous granuloma" which is synonymous with "Schüller-Christian disease", "lipid granuloma", "normocholesteremic xanthomatosis."

(3) Extracellular *precipitation* and crystallization of cholesterol. Such a process is the result of local changes in the physical properties of the tissue. It is not the result of increased cholesterol supply by the serum or of increased cholesterol synthesis. Example, arteriosclerosis of old age. Chronic inflammation of the gallbladder (so-called strawberry gallbladder).

In the following discussion and classification of xanthomatous diseases only those clinical syndromes will be considered in which an intracellular accumulation of cholesterol, *i.e.*, foam cell formation is found. The foam cell is the same in its histological aspect, whether it originates by cholesterol infiltration from a hypercholesteremic serum or whether it is formed by increased intracellular cholesterol synthesis. The latter mechanism takes place without hypercholesteremia. This difference in the mechanism of xanthoma cell formation is the rational for our classification of xanthomatous disorders. We distinguish three different clinical syndromes in the *hypercholesteremic group*: (1) essential familial hypercholesteremic xanthomatosis, (2) liver diseases with secondary skin xanthomata, (3) idiopathic and secondary hyperlipemia with eruptive xanthomata formation.

In the *normocholesteremic group* belong: (1) eosinophilic xanthomatous granuloma (synonymous with Schüller-Christian's disease, lipid granuloma and normocholesteremic xanthomatosis), (2) xanthoma cell formation in inflammatory tissue and in tumors.

For the exact clinical diagnosis, a chemical analysis of the serum is necessary together with a histological examination of the tissue. The normal value of lipids in milligrams in 100 c.c. of serum is as follows:

Total cholesterol	150-260
Free cholesterol	40- 70
Cholesterol ester	110-190 (70-75% of total cholesterol)

Method of Schoenheimer and Sperry

Total phospholipids	150-250 (determination of total lipid phosphorous $6-10 \times 25$ )
Saponifiable phospholipids	
Lecithin and cephalin	110-130 (cephalin present only in small amounts in serum; lecithin is the main part of the saponifiable phospholipids)
Sphingomyelin	10-50
	Method of Schmidt and Thannhauser
Total fatty acids	200-500
	Method of Stoddard and Perry
Neutral fat	
	Evaluation according to the formula of Thannhauser and Rheinstein
Cerebrosides	traces
	Method of Ottenstein, Schmidt and Thannhauser

### HYPERCHOLESTEREMIC XANTHOMATOSIS

#### A. FAMILIAL HYPERCHOLESTEREMIC XANTHOMATOSIS. ESSENTIAL HYPERCHOLESTEREMIC XANTHOMATOSIS

1. *Xanthoma (xanthelasma of the eyelids and tubercous and plain xanthoma of the skin.*
2. *Tendon xanthoma.*
3. *Tubercous and plain xanthoma of the skin, together with tendon xanthoma.*
4. *Xanthoma of the arterial intima and endocardium (atheroma) together with skin and tendon xanthoma.*
5. *Familial hypercholesteremia. "Forme fruste" of familial hypercholesteremic xanthomatosis.*

Magendantz and Thannhauser (1938), as well as Carl Mueller (1939), demonstrated that these five clinical features of essential familial hypercholesteremic xanthomatosis may be observed singly or in various combinations. The integration of these symptoms into a clinical syndrome was previously not conceived although many single cases were reported, mainly in the dermatological literature. In the group of familial hypercholesteremic xanthomatosis, other organs such as the brain, meninges, bone, liver, spleen and lymph glands are not involved. The involved organs are the skin, tendons, arterial intima and endocardium.

The color of the skin xanthoma is orange-yellow. The preferred locations are the eyelids, extensor surface of elbows, and the buttocks. The lesions do not appear on the face, neck or trunk. In rare cases, fleshy, colorless xanthomata of the subcutaneous tissues of the fingers or buttocks occur simultaneously with the orange-yellow skin xanthomata. The skin xanthomata of the familial group are permanent and do not disappear.

The tendon xanthomata are intimately connected with the tendon itself. The overlying skin is not involved or discolored. The tendon xanthomata are, therefore, often confused with the subcutaneous nodules of rheumatoid arthritis.



Familial hypercholesteremia may occur only as a monosymptomatic feature of this group, the so-called "forme fruste" and may cause atheroma formation in the coronary vessels resulting in coronary thrombosis. Not infrequently this occurs in young people of such families. Familial hypercholesteremia as a monosymptomatic feature (forme fruste) of familial hypercholesteremic xanthomatosis apparently occurs much more frequently than it was thought by Thannhauser and Magendantz in their first description. The diagnosis of "forme fruste" (familial hypercholesteremia) can only be secured by examination of the serum of several members of such a family for hypercholesteremia. Whether arcus senilis should be added to the characteristic symptoms of this group remains questionable. The expression of Stecher, "genetic" hypercholesteremia is not well-chosen since the genes do not transmit hypercholesteremia itself but probably transmit an enzymatic peculiarity which leads to familial hypercholesteremia. In analyzing family trees of this disorder, it became evident that the skin, tendons and blood vessels may be interchangeably involved in members of the same family. The inheritance is supposed to be dominant (Wilkinson and co-workers; Adlersberg and co-workers).

The chemical partition of the serum lipids in this group shows high values, mainly of cholesterol and cholesterol esters. The total cholesterol is increased 2 to 5 times the normal value. The cholesterol esters are present in normal proportion, *i.e.*, 70 to 75 per cent of the total cholesterol. The total phospholipids as well as the neutral fat are normal or only slightly increased. Rare cases exhibiting fleshy xanthomata show somewhat higher figures of neutral fat in the serum.

*The histological examination* of skin xanthomata of the hypercholesteremic familial group reveals an accumulation of foam cells beneath layers of the cutis surrounded by fibromatous tissue. Other cellular elements such as leukocytes, lymph cells or plasma cells are sparse. Eosinophilic cells are usually not present. In some areas the xanthoma cells arise in the vicinity of small blood vessels.

The tendon xanthomata are interwoven with the tendon tissue. Foam cells and fibroblasts are found in a tight fibrous tissue. Giant cells, as well as leukocytes and lymphocytes, are present only in small numbers.

The xanthoma of the arterial intima is slightly elevated and consists of an accumulation of foam cells in or beneath the intima. Fibrous or cellular reaction between the layers or nests of foam cells is inconspicuous in the first phase of the development of arterial xanthoma.

*Is there a pathogenic connection between familial hypercholesteremia and arteriosclerosis?*

Virehow, one hundred years ago in his discussion with Rokitsansky, distinguished two different alterations of the arterial wall, namely, (1) accumulation of fatty substances in the intima (Intima Verfettung), (2) alteration of the structural tissues and of the elastic ground substance of the deeper layers. In the widened tissue spaces plasma fluid secondarily accumulates and fatty material is precipitated in the loosened tissue spaces. At the same time a cellular inflammatory reaction takes place in the involved part of the arterial wall.

According to Virchow, this latter sequence of changes in the arterial wall leads to arteriosclerosis. They are not preceded by accumulation of fat in the intima. Accumulations of fat in the intima (Intima Verfettung) is not the first phase of arteriosclerosis. Unfortunately, Virchow coined the name "endarteritis deformans" for arteriosclerosis. This designation, as well as Virchow's interpretation of the inflammatory reaction in the arteriosclerotic blood vessel, was not accepted and, thus, the fundamental interpretation of Virchow of the pathogenesis of arteriosclerosis was for a time discarded. Aschoff, fifty years later, tried to revive Virchow's conception. Aschoff, influenced by his observations in autopsies of young soldiers in World War I and by the studies of his pupil, Anitschkov, claimed that the accumulation of fat, especially that of cholesterol, may already appear in the arterial wall of young persons and later in life develop into the arteriosclerotic processes as interpreted by Virchow. Leary extended Aschoff's ideas and applied them to clinical medicine asserting that the intake of too much cholesterol-containing food leads to the first phase of arteriosclerosis, *i.e.*, accumulation of cholesterol in the intima cells. The deeper layers of the vascular wall gradually become involved in the later phases of the process. This conception of arteriosclerosis as a continuous process starting with accumulation of cholesterol and fatty substances within the cells of the intima and consecutively involving the elastic structures of deeper layers, brought up the question of whether or not xanthoma (atheroma) formation of the inner lining of the arteries as observed in the clinical syndrome of familial hypercholesteremic xanthomatosis, is the first phase of arteriosclerosis.

In the author's opinion, the vascular xanthoma (atheroma) of familial hypercholesteremic xanthomatosis is a localized process similar to that of the skin xanthoma. Stretches of layers of xanthoma cells pile up over or beneath the inner lining of the blood vessel. At the beginning there is little cellular or fibroblastic reaction. The elastic ground substance is not primarily affected. The atheroma may soften and cause coronary occlusion. It may develop into fibrous scar tissue and sclerosing changes of the deeper layers may result but it always remains a localized process.

Arteriosclerosis, in contrast to familial hypercholesteremic xanthomatosis, primarily involves the elastic structures and their ground substance. The precipitation of fatty material, especially of cholesterol in arteriosclerosis, is a secondary process. It is not dependent upon the cholesterol level of the serum but is caused by the physical properties of the altered tissue as well as by the physical properties of the colloidal solution of cholesterol\* and fatty substances imbibing the altered structures of the vascular walls. Secondary to this process, foam cells may appear simultaneously with the cholesterol imbibition also in the deeper layers of the sclerotic vessels.

\* The colloidal solution of cholesterol in serum is influenced by the physical properties of other substances also present in the serum in a colloidal stage such as phospholipids and proteins. Since proteins form with lipids colloidal agglomerates but no definite stoichiometric compounds, the physical condition of the various protein moieties (different in structure, size and mobility) may affect the stability of the colloidal solution of cholesterol in serum.

However, it remains an open question of what primarily causes the alteration of the elastic structures and their ground substance in arteriosclerosis. The pathogenesis of the arteriosclerotic process is apparently not uniform in all instances. Some authors consider a wear and tear process dependent upon constitutional hereditary factors occurring earlier or later in life as the cause. Areas of the larger arteries which are mainly exposed to the impact of the systolic ejection are the preferential subjects to wear and tear. Others (Winternitz, Schlichter) demonstrated changes in the vasa vasorum of the larger vessels suggesting that a diminished oxygen supply alters the vital conditions of the vascular tissue.

From the clinical point of view, the following observations are against the assumption that the cholesterol accumulation in the intima, as observed in familial hypercholesteremic xanthomatosis, is the first phase of arteriosclerosis. (1) The clinical symptom common to familial hypercholesteremia and arteriosclerosis is the occurrence of coronary involvement in both disorders. Coronary disease, however, is not pathognomonic for the assumption of arteriosclerosis; it may occur in a variety of vascular disorders. (2) Clinical features of premature development of arteriosclerosis are not found in patients with familial hypercholesteremic xanthomatosis. Members of such families, if they do not die of coronary thrombosis, may live to an advanced age without developing generalized arteriosclerosis. The author has observed patients, fifty to seventy years of age, with familial hypercholesteremia who showed no more features of arteriosclerosis than other patients of the same age group. (3) The cholesterol content of the patients with arteriosclerosis or their families is usually within normal range in contrast to persons with familial hypercholesteremia. (4) The pathogenesis of atheroma formation in patients with familial hypercholesteremic xanthomatosis should not be confused with arteriosclerotic changes in diabetes. In the first condition we are dealing with a disturbance of cholesterol formation and excretion causing localized atheroma formation, while in diabetes a disturbance of the carbohydrate metabolism is noxious to the nutrition of tissues, especially to that of the vascular system. In diabetes, true arteriosclerosis may also develop in cases in which hyperlipemia and hypercholesteremia are not present. For these reasons it may be concluded that the clinical syndrome of familial hypercholesteremic xanthomatosis, including its "forme fruste" (familial hypercholesteremia), is a disease entity in itself different from arteriosclerosis (atherosclerosis).

Familial hypercholesteremia is caused by an imbalance of cholesterol synthesis and cholesterol excretion. Arteriosclerosis (atherosclerosis) has no primary etiological connection with cholesterol metabolism. It is a disorder affecting the elastic structures and the ground substance of the vascular wall with secondary cholesterol imbibition and precipitation of cholesterol in the altered tissue.

We conform with the fundamental concepts of Virchow, namely, that the accumulation of fatty substances in the intima (*Intima Verfettung*) as occurring in familial hypercholesteremia and the alteration of the vascular wall in arteriosclerosis are two different diseases which are neither etilogically nor chronologically correlated.

The clinical implications of this concept are evident. (1) Restriction of chole-

terol intake will not basically influence the development of arteriosclerosis since cholesterol precipitation in the sclerosed arterial wall is caused by a physico-chemical change of the colloidal state of cholesterol in the serous fluid imbibing the sclerosed vascular tissue. This physicochemical process is independent of the concentration of cholesterol in the serum. (2) Restriction of animal cholesterol in the diet is, however, desirable in familial hypercholesteremia because a metabolic imbalance of cholesterol synthesis and excretion is the cause of the accumulation of cholesterol in the serum in this condition.

It has to be kept in mind that even the strictest dietary measures excluding all animal cholesterol will rarely effect normal cholesterol levels of the serum in familial hypercholesteremia. Dietary restriction of animal cholesterol eliminates only the exogenous quota of cholesterol metabolism, *i.e.*, 200 to 300 mg. daily in a mixed diet. The endogenous quota of cholesterol, *i.e.*, cholesterol synthesis in the organs, continues in spite of the diminished intake. The endogenous quota is much higher than the amount of cholesterol provided by a normal diet. For this reason, dietary restriction of cholesterol in the treatment of familial hypercholesteremia will be helpful but will not completely control this metabolic disorder.

#### B. HYPERCHOLESTEREMIC XANTHOMATOSIS SECONDARY TO LIVER DISEASE

##### 1. *Xanthomatous biliary cirrhosis. Pericholangiolitic biliary cirrhosis with tuberous and plain skin xanthomata*

Xanthomatous biliary cirrhosis is characterized by the following clinical features: (a) chronic jaundice of several years duration, (b) enlargement of the liver and spleen, (c) tuberous and plain skin xanthomata which appear on the whole body including the creases of the hands, (d) cholesterol and cholesterol esters together with the phospholipids in the serum are enormously elevated (6 to 10 times the normal value). At the onset of the disease, the proportion of the cholesterol esters to the total cholesterol is normal; in later phases of the disease the proportion of esters diminishes. The phospholipid value remains elevated during the entire course of the disease, (e) the serum is clear and transparent; it is never milky. The serum values for neutral fat are normal or very low.

The disease has a slow course. Itching of the skin and jaundice are the first symptoms. Xanthomata usually develop one-half to one year later. The liver and spleen are considerably enlarged. The bile flow to the intestines is never completely interrupted. Urobilin is always present in stools and urine. The main complaint is unbearable itch. In the first years of the disease the patient is able to maintain his daily routine of work. After 4 to 7 years duration, death is caused by profuse bleeding from esophageal varices. The total cholesterol of the serum decreases toward the end of the disease. In contrast to the findings at the onset of the disease, the percentage of the ester of total cholesterol is markedly diminished. The total phospholipids remain high.

Up to the present time, xanthomatous biliary cirrhosis has been observed only in females. If a similar clinical syndrome is seen in males another kind of liver disease should be suspected. In contrast to familial hypercholesteremic xantho-



matosis, the disease is not hereditary. The etiology is unknown. It is apparently different from epidemic infectious hepatitis.

In biopsies of early stages of xanthomatous biliary cirrhosis, MacMahon and Thannhauser demonstrated that pericholangiolitic inflammatory obliteration of the smallest interlobular bile capillaries and of the junction ducts cause an obstructive type of jaundice. The large bile ducts are not involved in the inflammatory process. In later stages cirrhotic changes develop and replace the parenchymatous tissue similar to that seen in portal cirrhosis. Only biopsies in the earlier phases of the disease clearly show the initial pericholangiolitic inflammatory process. Addison and his pupils reported xanthomata of the inner lining of the large bile ducts. In our first description of xanthomatous biliary cirrhosis we believed that xanthomatous changes of the large bile ducts caused xanthomatous biliary cirrhosis. This suggestion, based on the autopsy findings of Addison and his pupils, can not be maintained since xanthomatous involvement of the large bile ducts was not found in our biopsies and autopsies. In rare cases, xanthomata of the inner lining of the bile duct (similar to the skin xanthomata) may develop but they are the result of the primary pericholangiolitic inflammatory process and not the cause of this type of biliary cirrhosis. Thannhauser assumes that the enormously high cholesterol and phospholipid content of the serum is not only caused by the inflammatory obstruction of the finest interlobular bile ducts but is also a result of an increased production of these lipids in the diseased liver of this peculiar syndrome.

2. *Rare cases of chronic liver disease with hypercholesteremia and skin xanthomata*

(a) *Hemochromatosis with hypercholesteremia and skin xanthomata.* Skin xanthomata in patients with hemochromatosis are rare incidents. The mechanism of their pathogenesis is not clearly understood. They may result from hypercholesteremia coincident with hyperlipemia due to chronic hemochromatous pancreatic cirrhosis or the hemochromatous liver cirrhosis may involve the finest bile capillaries. In the case of the first suggestion hyperlipemia, *i.e.*, increase of neutral fat, together with hypercholesteremia should be found; in the case of the second hypothesis only hypercholesteremia, but no increase of neutral fat, should be present. In the few cases observed, determinations of neutral fat are not reported.

(b) *Postoperative obliteration of the common bile duct, hypercholesteremia and skin xanthomata.* Postoperative obstruction of the common bile duct after injury of the common duct during the operation is not uncommon. Hypercholesteremia of a moderate degree consequently develops. In rare instances, however, the hypercholesteremia is very high and skin xanthomata may develop, as in two cases reported from the Mayo Clinic.

C. HYPERCHOLESTEREMIA IN HYPOTHYROIDISM

Hypercholesteremia in hypothyroidism was first reported by Heekschel (1925). The serum of patients with hypercholesteremia in hypothyroidism is transparent. In the few cases in which skin xanthomata together with hypothyroidism were observed, a creamy serum was noted. It is, therefore, questionable if in these rare cases the hyperlipemia, *i.e.*, the increase of neutral fat, was a feature of hypo-



thyroidism or was primarily present as "idiopathic hyperlipemia" but later complicated by hypothyroidism. Usually, hypothyroid patients, even if high values of cholesterol are found, do not show a marked increase of neutral fat or phospholipids in the serum.

The cause of the increase of the cholesterol (cholesterol esters are present in normal proportion to total cholesterol) in the serum of hypothyroid patients is not definitely known. The enzymatic processes leading to cholesterol synthesis in the organism are influenced by various causes. One of these processes seems to be connected with the function of the thyroid since hyperthyroidism is associated with low cholesterol values while hypothyroidism produced a marked increase of cholesterol in the serum. Thyroid medication lowers the cholesterol values of the serum.

#### HYPERLIPEMIA (ACCUMULATION OF NEUTRAL FAT IN SERUM) WITH SECONDARY "ERUPTIVE" XANTHOMATA

##### A. IDIOPATHIC HYPERLIPEMIA

##### 1. *Idiopathic (familial) hyperlipemia in children with hepatosplenomegaly and "eruptive" xanthoma (hepatosplenomegale lipidose of Bürger and Grütz)*

The hyperlipemic serum is creamy and not transparent. This phenomenon is due to an increase of neutral fat of 5 to 20 times that of normal serum. The concurrent increase of cholesterol and phospholipids is less marked. These lipids are increased only 2 to 5 times that of normal. The serum becomes milky if the increase of neutral fat exceeds 1200 mg. in 100 c.c. of serum (normal 0 to 200 mg. %).

The clinical syndrome of idiopathic hyperlipemia in children is characterized by the following features: (a) creamy serum with enormous increase of neutral fat. This abnormality is more often accidentally discovered since hyperlipemia, as such, does not cause any discomfort. Familial incidence of hyperlipemia is only observed in a few of the reported cases (Holt). (b) Liver and spleen are enlarged. (c) Jaundice is never present. (d) Attacks of abdominal colic may be observed occasionally. (e) Eruptive skin xanthomata. The eruptive xanthomata of the hyperlipemic group are different in their appearance, as well as in their localization, from the xanthomata of the familial hypercholesteremic group. The eruptive xanthomata are surrounded by a small red halo which already macroscopically indicates their inflammatory nature. The eruptive xanthomata are distributed all over the body. They may even be seen on the mucous membranes of mouth and gums. They are not permanent and appear and disappear corresponding to the level of neutral fat in the serum. An eruption of xanthomata is not an invariable symptom of idiopathic hyperlipemia.

The histology of the eruptive xanthoma is different from that of the xanthoma occurring in the familial hypercholesteremic xanthomatosis. In the eruptive xanthoma the cellular elements of the inflammation are most conspicuous while foam cells are sparse in the inflammatory tissue. The foam cells are not congre-

gated in nests or lines as in the tuberous and plain xanthoma of the familial hypercholesteremic group. Also, in the enlarged liver and spleen the number of foam cells is relatively small and only encountered after prolonged search. It is remarkable that the content of neutral fat in the inner organs is not increased in spite of its enormous increase in the serum of these patients.

The etiology of idiopathic hyperlipemia is not known. The behavior of idiopathic hyperlipemia is similar to that of postprandial hyperlipemia because it is dependent upon the exogenous fat supply, *i.e.*, from the fat of the food. A fat-free diet reduces the fat content of serum to almost normal values. It may be suggested that neutral fat in idiopathic hyperlipemia is retained in the serum and only sluggishly permeates the capillaries. For this reason we designated this type of hyperlipemia as "retention hyperlipemia." The experiments with feeding of fat-containing radioactive iodine in patients with idiopathic hyperlipemia support this theory (Stanley and Thannhauser).

*2. Idiopathic hyperlipemia in adults with and without secondary eruptive xanthomata occasionally accompanied by slight glycosuria and hepatosplenomegaly*

The idiopathic hyperlipemia of the adult in its symptomatology is not essentially different from the symptoms occurring in idiopathic hyperlipemia of children. Lipemia retinalis is reported in some adult cases. Jaundice is never present. The course of idiopathic hyperlipemia in adults is mostly without symptoms if eruptive xanthomata do not appear. The presence of hyperlipemia in these cases is accidentally discovered in a routine blood examination. A familial occurrence in adults has not yet been reported. Hepatosplenomegaly and abdominal colic usually are not observed. Some patients of the adult variety of idiopathic hyperlipemia, however, may show a tendency to a slight elevation of blood sugar or to slight glycosuria. Probably, for this reason, these hyperlipemic cases were erroneously registered in the literature as "xanthomata diabeticorum." There is, however, in many cases not even a slight glycosuria found. A diabetic condition is not the cause of idiopathic hyperlipemia. Secondary hyperlipemia with eruptive xanthomata, however, may indeed be precipitated by a severe untreated diabetic condition but hyperlipemia, as well as eruptive xanthomata, disappear in diabetic cases as soon as the diabetic condition is balanced by insulin treatment irrespective of the fat content of the supplied food. In contrast to this behavior of diabetic patients, insulin does not influence the hyperlipemia in idiopathic hyperlipemia. In these cases the level of neutral fat in the serum is not reduced by insulin but is reduced to almost a normal level within a few weeks by a diet low in fat (10 to 20 gm.). The hyperlipemia reappears as soon as fat is again supplied with the food (see Table I). Such a behavior reveals the fundamental difference in the etiology of hyperlipemia in both diseases. In idiopathic hyperlipemia the fat is retained in the blood stream probably because it passes sluggishly through the capillaries (retention hyperlipemia). In severe untreated diabetes hyperlipemia occurs as a result of insufficient carbohydrate disinter-

gration as a symptom of increased fat transport to the organs of metabolism. In idiopathic hyperlipemia, the hyperlipemia is corrected by a fat-free diet; insulin is without effect. In diabetes, however, insulin balances the diabetic disturbance and simultaneously results in the disappearance of hyperlipemia (transport hyperlipemia). The appearance and the localization of the eruptive xanthomata in idiopathic hyperlipemia in adults, as well as their histology, is not different from that in children.

#### B. SYMPTOMATIC HYPERLIPEMIA WITH SECONDARY ERUPTIVE XANTHOMATA

##### 1. *Hyperlipemia with secondary eruptive xanthomata in severe untreated diabetes*

Symptomatic hyperlipemia in cases of severe untreated diabetes has been known for a long time and was more frequently observed before insulin treatment was introduced. At present the administration of insulin in due time pre-

TABLE 1  
*Lipid analyses of serum in a case of "idiopathic hyperlipemia" in an adult*

	2-12-46	AFTER LOW-FAT DIET 3-29-47	6-24-46		9-19-46	1-10-47		6-25-46
	mg. %	mg. %	mg. %		mg. %	mg. %	mg. %	
Total fatty acids	5196	480	688	The patient	1171	1310	3100	The eruptive
Neutral fat	4477	275	350	gradually	—	954	2525	xanthomata
Total cholesterol	693	175	292	stopped	242	318	375	gradually
Free cholesterol	323	58	76	keeping to	85	120	150	disappeared
Cholesterol present as esters	396	117	216	his diet	185	181	225	leaving a
% of Total	53	67	74		—	—	60	brownish-red
Total phospholipids	810	195	250		—	318	351	skin discoloration.
Lecithin and cephalin	685	175	220		—	—	—	The xanthomata
Blood sugar	206	130	124		120	—		had not yet
Urine sugar	0.2 gm. Negative	Negative	Negative		Negative	Negative	Negative	reappeared at
								5-19-47.

vents a severe hyperlipemic condition. Eruptive xanthomata in cases of severe diabetes are now very rarely seen for this reason. The appearance and histology of eruptive xanthomata are the same as already described in the paragraph dealing with idiopathic hyperlipemia. The eruptive xanthomata in diabetes, in contrast to those in idiopathic hyperlipemia, do not react to restriction of fat in the diet but disappear simultaneously with the hyperlipemia as soon as the disturbance of the carbohydrate metabolism is balanced with insulin. It is suggested that hyperlipemia in diabetes is the result of increased fat transport to the organs of metabolism and is secondary to the disturbance of carbohydrate metabolism (transport hyperlipemia). Some authors believe that hyperlipemia by itself causes arteriosclerosis in diabetic patients. This opinion seems to be not quite justified since arteriosclerosis is not a feature in persons with idiopathic hyperlipemia although hyperlipemia in these persons lasts a lifetime. The frequency of arteriosclerosis in diabetes, however, seems primarily connected with the disturbance

of the carbohydrate metabolism which apparently results in considerable damage to the elastic structures of the vascular wall producing the features of arteriosclerosis, just as in arteriosclerosis uncomplicated by diabetes (see page 000). Fatty substances and cholesterol precipitate secondarily in the altered tissue of the arterial wall.

## 2. *Hyperlipemia in acute and chronic pancreatitis and eruptive xanthomata*

In acute pancreatitis the increase of neutral fat and cholesterol in the serum is a transient condition only observed during the first days. In chronic pancreatitis the increase of lipids is not observed in all cases, but it may be considerable and may lead to an eruption of xanthomata. The cause of the hyperlipemia in pancreatitis is not well understood. The suggestion of a "lipocaic" substance in the pancreas (Dragstedt) is not yet proven. It was shown (Ottenstein, Schmidt and Thannhauser) that "lipocaic pancreas extract" contains glycerolphosphorylcholine, a metabolite of lecithin which has like choline lipotropic activity. The appearance of the eruptive xanthomata in chronic pancreatitis is the same as that in other hyperlipemic conditions.

## 3. *Hyperlipemia in glycogen storage disease (von Gierke's disease) and eruptive xanthomata*

Creamy serum, *i.e.*, hyperlipemia, was observed in some cases of von Gierke's disease. Eruptive xanthomata in this disease were reported by Beumer. The cause of hyperlipemia in von Gierke's disease is comparable to the etiology of hyperlipemia in severe untreated cases of diabetes. The disturbance of the carbohydrate metabolism in both diseases involves entirely different phases of the enzymatic system concerned with the carbohydrate metabolism, but the effect upon the fat metabolism is the same in both instances. In both diseases not enough carbohydrate is available in its metabolisable form. Fat has to be mobilized from its depots and hyperlipemia (transport hyperlipemia) results. The degree of hyperlipemia in von Gierke's disease is dependent on the severity of the disturbance of the carbohydrate metabolism. In von Gierke's disease, corresponding to the level of neutral fat in the serum, a very large fatty liver is found. This is in contrast to idiopathic hyperlipemia in which fat deposition in the liver does not coincide with the accumulation of fat in the serum.

## 4. *Hyperlipemia in lipid nephrosis*

Hyperlipemia is observed in genuine lipid nephrosis as well as in certain phases of chronic glomerulonephritis. In these conditions neutral fat is increased in the same proportion as the total cholesterol. The cause of hyperlipemia in nephrotic conditions is interpreted differently. Some authors assume that hyperlipemia is the result of the decrease of the serum proteins in these conditions. Others believe that the kidney itself regulates by nervous impulses the transportation of fat from its depots. Only in one case of nephrotic hyperlipemia have eruptive xanthomata been reported.



### NORMOCHOLESTEREMIC XANTHOMATOSES

#### A. EOSINOPHILIC XANTHOMATOUS GRANULOMA SYNONYMOUS WITH SCHÜLLER-CHRISTIAN SYNDROME, LIPID GRANULOMA, EOSINOPHILIC GRANULOMA, RETICULOGRANULOMA, ESSENTIAL XANTHOMATOSIS OF THE NORMOCHOLESTEREMIC TYPE

The lesion of eosinophilic xanthomatous granuloma (Schüller-Christian syndrome) is histologically granulomatous in nature. The yellow-grayish color of the afflicted tissue is the result of an accumulation of xanthoma (foam) cells in this tissue. There is no other systemic granulomatous disease known in which foam cells develop as a characteristic feature of the granulomatous lesions. For this reason, eosinophilic xanthomatous granuloma is classified under the normocholesteremic xanthomatoses. The normal cholesterol content of the serum in this disorder signifies that the accumulation of cholesterol within the xanthoma cells of this systemic lesion is not due to an imbalance of the intermediary cholesterol metabolism, as in hypercholesteremic familial xanthomatosis, but is caused by an intracellular metabolic disturbance of certain cells of this particular granuloma. Thannhauser and Magendantz (1938) elaborated the clinical syndrome of eosinophilic xanthomatous granuloma, at that time designated by these authors as essential xanthomatosis of the normocholesteremic type. They demonstrated that this disorder may affect only one single organ as monosymptomatic form involving only skin or bone, or it may simultaneously appear in various combinations in several organs as in Schüller-Christian syndrome. The generalized form of this disorder is mainly observed in infants involving skin, osseous system, brain, meninges, lungs, pleura, lymph glands, liver and spleen.

The histological studies of Fraser (1934) and of Farber (1944) and especially the conception of Holm, Teilum and Christensen (1944) of the different histological phases of the lesion of eosinophilic xanthomatous granuloma has considerably advanced our understanding of the disorder. Teilum and co-workers demonstrated that the natural history of the granulomatous lesion comprises the following phases:

1. *The hyperplastic proliferative phase.* Proliferation of reticulum cells and histiocytes dominate the histological picture in this phase. Some eosinophilic cells in a sea of reticulum cells and histiocytes may already appear in this first stage of the lesion.

2. *The granulomatous phase.* Numerous eosinophilic cells and leucocytes become apparent. Giant cells and incipient lipid accumulation in some reticulum cells are characteristic of this phase. An increase of blood vessels and fibrils also is observed.

3. *The xanthomatous phase.* Intracellular lipid material becomes definitely evident in the cytoplasm of some reticulum cells which assume the shape of macrophages. The cytoplasm of these cells become "foamy" in appearance finally developing the characteristics of xanthoma cells.

4. *The fibrous phase.* The xanthoma cells and endothelial cells are replaced by fibroblasts and connective tissue with the result that the lesions show an indis-



erminate arrangement of fibrous tissue of fibroblasts and of some foam cells. Extracellular lipid deposits are rarely seen.

These four phases show no strict demarcation during the course of the disease. The histological features may overlap considerable. It is understandable why a biopsy taken in the early development of the lesion which does not show xanthoma cells but shows reticulo-endothelial proliferation or numerous eosinophilic cells is, for this reason, designated as reticulo-endotheliosis or as a granuloma characterized by proliferation of eosinophilic cells. It should however, be emphasized again that reticulo-endothelial proliferation, as well as the appearance of eosinophiles in the early phases, is no less characteristic of the lesion as the xanthoma cell formation in a later phase.

The process which causes the formation of xanthoma (foam) cells in this peculiar granuloma is of special interest. In contrast to the hypercholesteremic xanthomatoses, the xanthoma cell in eosinophilic xanthomatous granuloma (Schüller-Christian syndrome) develops independently of the cholesterol content of the serum. A normal level of cholesterol, phospholipids and neutral fat is an outstanding clinical feature of this disease. Thus, the marked accumulation of cholesterol in certain cells of the granuloma takes place without increased supply from the blood stream. The suggestion of cholesterol infiltration from the blood stream as an etiological mechanism of xanthomata formation in this instance is, therefore, not acceptable. Another suggestion (S. Farber) which assumes that the intracellular accumulation of cholesterol derives from the detritus of focal necrosis in the granulomatous tissue, is not supported by the following observations: (1) Granulomatous lesions of the skin, like those in Hodgkin's disease, mycosis fungoides or infectious granuloma show large areas of macroscopically visible necrotizing processes but no foam cell formation. In contrast to these granulomatous diseases, one rarely, if ever, finds necrotic areas in eosinophilic xanthomatous granuloma. Especially in the skin manifestations of this disease (xanthomata disseminata), xanthoma formation is outstanding but no focal necrosis is visible. (2) A shift of a chemical constituent from one cell which supposedly has undergone dissolution (necrosis) to another cell macrophagic in character, will not cause a measurable increase of this substance in the tissue, presupposing that an adequate specimen (0.5 to 1 gr.) of this tissue is used for the quantitative chemical analysis. Chemical analyses of tissue in the xanthomatous phase of eosinophilic xanthomatous granuloma show an increase of cholesterol from 10 to 20 times that of normal tissue (see Table II). This enormous increase of cholesterol in an analyzed specimen of tissue of this kind of granuloma can not be considered as originating from cholesterol infiltration derived from small areas of local necrosis.

On the basis of these considerations, together with the figures of the chemical analysis, one comes to the conclusion that the cholesterol originates intrinsically in those cells of the granuloma where it is found. These cells, mostly of reticular and histiocytic origin, have maintained the functional possibilities of undifferentiated embryonal reticulum cells (embryonal fat cells of Waldeyer) to form various kinds of lipids including cholesterol. During the course of the disease,

formation and retention of cholesterol in some undifferentiated reticulum cells takes place whereby these cells assume the appearance of macrophagic cells and develop gradually into xanthoma (foam) cells. This process is an intracellular enzymatic process and not the result of a general disturbance of the intermediary cholesterol metabolism.

Eosinophilic xanthomatous granuloma shows the following features, singly or in various combinations:

1. *Skin lesions.* (a) Xanthomata disseminata of the skin. The fully developed skin xanthomata of this disorder are lemon or chamois in color; in a later phase they are maroon in hue. The lesions are disseminated (xanthoma disseminata) over the whole body. They are raised, discrete or clustered in smooth patches or arranged in ridges and furrows. They may vary in size from the size of a pinhead to the size of a walnut; they do not ulcerate. The preferred location is within the axillae, around the neck, face, eyelids and in the antecubital fossae. They

TABLE 2

*Lipid partitions in specimens of tissue during the xanthomatous phase of eosinophilic xanthomatous granuloma*

TISSUE	TOTAL CHOLES- TEROL	FREE CHOLES- TEROL	CHOLES- TEROL ESTERS	TOTAL PHOSPHO- LIPID	SPHINGO- MYELIN	LECTI- THIN	TOTAL FATTY ACID	NEUTRAL FAT
	%	%	%		%	%	%	%
Diseased lymph node . . . . .	17.90	2.20	15.70	6.4	Trace	—	—	—
Normal lymph node . . . . .	0.60-2.30	0.50-1.10	0.20-1.20	5.5-11.0	0.3-07	—	—	—
Dura mater . . . . .	18.58	3.20	15.30	—	—	1.6	—	—
Skin . . . . .	4.55	3.66	0.89	—	—	—	3.64	—
Normal skin . . . . .	0.15-0.30	—	—	—	—	—	—	—
Diseased liver . . . . .	7.25	4.55	2.70	7.4	—	—	9.05	0.71
Normal liver . . . . .	1.10-2.60	1.50-2.10	0.45-0.55	9.0-11.0	—	—	8.60-13.0	1.4-4.0

may also be found as plain or tuberous xanthoma on the scalp or on the mucous membranes of the mouth or bronchi. It is possible to discriminate xanthomata disseminata from the skin xanthomata of the hypercholesteremic familial group by color, as well as by their localization. Biopsies show an abundance of foam cells and histiocytes in the subcutaneous tissue. Scattered multinucleated giant cells are more conspicuous than eosinophilic cells. In infants, a discrete orange-brown disseminated xanthoma is described which is erroneously classified as nevo-xantho-endothelioma. These lesions may disappear in later life. Other organs may not become involved. The histology of the lesions is the same as in xanthomata disseminata and is granulomatous in nature.

(b) Petechiae-like lesions of the skin. These flat, reddish-purple lesions are of the size of a pinhead or a little larger. They may disappear leaving behind a spot of brownish discoloration. They rarely develop into a tuberous lesion of the disseminata type. Petechiae-like lesions may occur, however, together with fully

developed lesions of xanthomata. The dominating histological feature of the petechiae-like lesions is an accumulation of reticulum cells and histiocytes. They seem to develop from the outer wall of a capillary with hemorrhagic exudation in the connective tissue.

2. *Osseous lesions.* The osseous lesions appear as osteolytic cyst-like defects by x-ray. They may be seen in any part of the osseous system. The skull was erroneously considered to be the most frequently involved part of the skeleton. A definite diagnosis of such an osteolytic defect can only be made by biopsy. The histological examination of the lesion shows a granulomatous tissue with reticulum cells and nests of eosinophilic cells. Some authors believed that they had discovered a specific, hitherto not described, bone disease and named it "eosinophilic granuloma of bone" since only the bones were affected in these cases and a prevalence of eosinophilic cells was found in the granuloma at the time of biopsy. It is, however, evident that osseous involvement may occur as a mono-symptomatic form of eosinophilic xanthomatous granuloma (Schüller-Christian syndrome). The assumption that it is a new disease is not justified. The fibrous phase of the lesion develops in the bone earlier than in other organs. For this reason the xanthomatous phase may not become conspicuous.

3. *Lesions of meninges and brain.* Diabetes insipidus and exophthalmus are the most frequent features of meningeal and brain involvement. The granulomatous masses may cause features of intracranial pressure or, in rare instances, epileptic seizures. The xanthomatous phase of the granuloma is very conspicuous in these organs because it shows a yellow color of the lesion. Very frequently, but not always, defects of the skull are seen at the same time.

4. *Teeth.* In some cases the sockets of the teeth show yellowish tissue which may simulate an accumulation of pus at the root of a tooth. The histology of such tissue reveals eosinophilic xanthomatous granuloma.

5. *Lesions of lung and pleura.* The patients rarely complain of symptoms indicating involvement of lungs and pleura. X-ray examination of the lungs mostly in juvenile persons show a pattern very similar to that seen in miliary tuberculosis or diffuse fibrosis of the lung. Affection of the pleura by yellowish stripes of granulomatous tissue is only recognized after death. The histological examination of the lung mainly shows the fibrous phase of the granuloma with interspersed foam cells. In rare cases discrete granulomatous lesion in a bronchus is found which is only identified by its histology.

6. *Lesions of lymph glands, liver and spleen.* Hepatosplenomegaly with diffuse lymphadenopathy is present in juvenile patients, especially in the generalized form in infancy. In the cases of liver involvement, neither jaundice nor ascites are observed. The clinical diagnosis in juvenile cases with hepatosplenomegaly may be difficult if the characteristic skin or bone involvement is not present at the same time. In all these cases the diagnosis can only be made by biopsy. The histology of the lesion shows all phases of eosinophilic xanthomatous granuloma, namely, reticulo-histiocytic proliferation, nests of eosinophiles, giant cells, incipient intracellular accumulation of lipids or fully developed xanthoma cells and fibrosis.

As already mentioned, eosinophilic xanthomatous granuloma may affect only one single organ as skin or bone or it may implicate skin and brain (skin xanthomata and diabetes insipidus), or it may involve skin, meninges, brain, bone and lungs in various combinations (Schüller-Christian syndrome) or it may be observed, especially in infants and in early childhood, as generalized xanthomatous disease involving skin, meninges, brain, lungs, lymph nodes, liver and spleen.

7. *The generalized form* of this disorder in its first phase is, according to the opinion of many authors, identical with the acute reticulo-endotheliosis of *Letterer and Siwe*. The rapid fatal termination of this form of the disease prevents the development of the xanthomatous phase. This conception of the relation of Letterer-Siwe's disease to eosinophilic xanthomatous granuloma apparently is correct, since cases of acute reticulo-endotheliosis were observed in which the xanthomatous transformation of the lesions had already started before the infant died.

#### B. XANTHOMA (FOAM) CELLS IN INFLAMMATORY TISSUE AND IN TRUE TUMORS

##### 1. *Xanthoma cells in inflammatory tissues.*

a. Inflammatory tissue showing xanthoma cells, chronically inflamed gallbladder (so-called strawberry gallbladder), chronic salpingitis, osteomyelitis, necrotic areas of nodules of rheumatoid arthritis, cholesterol pneumonitis.

b. Inflammatory xanthoma of the breast.

c. Xanthoma cells in osteitis fibrosa cystica disseminata (fibrous dysplasia).

d. Intestinal lipodystrophy of Whipple. Xanthomatous transformation of the mesentery.

##### 2. *Xanthoma cells in tumors.*

a. Xantholipoma.

b. Xanthomatous polycystic lymphangioma.

c. Epithelial tumors with xanthoma cells.

Xanthoma cells may originate in inflammatory, fibromatous, sarcomatous or carcinomatous tissue. Corresponding to the number of reticular cells undergoing xanthomatous transformation, the tumor becomes more yellowish and appears as a xanthomatous tumor. A true blastoma, however, is never formed only by xanthoma cells.

The cause of the occasional occurrence of single xanthoma cells or nests of xanthoma cells in inflammatory or tumorous tissue is not known. Some investigators believe that infiltration of cholesterol from the blood stream or from necrotic areas of the tissue is the mechanism which results in these instances in xanthoma cell formation. Such a process may explain the xanthoma formation in some of these conditions if definite areas of necrosis are obvious. In cases, however, in which necrotic foci are not present, we assume that the development of foam cells in inflammatory and tumorous tissue originates by intracellular cholesterol formation in reticulum cells and histiocytes. This process would be analogous to the mechanism which causes the xanthoma cell formation in eosinophilic xan-

thomatous granuloma; namely, immature reticulum cells and histiocytes still undifferentiated and polyvalent in their enzymatic properties are able to form cholesterol and lipids within the cell and are, thus, gradually transformed into xanthoma (foam) cells.

*Literature:* Complete bibliography and photographs may be found in "Lipidoses: Diseases of the Cellular Lipid Metabolism" (second edition) by S. J. Thannhauser, M.D., Ph.D., Oxford University Press, New York, 1950.



## AN ULTRAVIOLET SPECTROPHOTOMETRIC METHOD FOR THE DETERMINATION OF $\Delta^{3,5}$ ANDROSTADIENONE-17 IN THE URINE\*

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The reported (1, 2, 3, 4) occurrence of large amounts of  $\Delta^{3,5}$  Androstadienone-17 in patients with adrenal cortical tumor and hyperplasia suggested to us that a relatively simple method for its determination, employing small amounts of urine, would be useful as a diagnostic tool for disorders of this type.

The method developed is based on the absorbing properties in the ultraviolet spectrophotometer of  $\Delta^{3,5}$  androstadienone-17. The 11-hydroxycorticosteroids were determined in a 200 ml. aliquot of a 24 hour urine sample, according to the method of Corcoran and Page (5). The unused residue was then subjected to a Girard separation and the ketonic fraction examined in the Beckman spectrophotometer. As will be shown below, the spectral data indicate that the observed absorption is due to  $\Delta^{3,5}$  androstadienone-17.

The spectroscopic examination of the ketonic fraction obtained from 5 normal individuals and 11 patients having no demonstrable adrenal cortical disease showed no evidence of the presence of  $\Delta^{3,5}$  androstadienone-17. Dobriner and coworkers (3) have reported the isolation of this substance from the urine of 4 out of 6 normal patients. These investigators, however, employed large quantities of pooled urines, collected over a prolonged period of time. The administration of 60 mgm. of adrenocorticotrophic hormone from the adenohypophysis, in 4 divided doses daily over a period of 2-3 days, to 4 individuals without overt adrenal disease failed to produce spectroscopic evidence of the presence of this steroid.

The spectra of the ketonic fraction obtained from the urine of 2 patients with adrenal hyperfunction, one with an adrenal cortical carcinoma and the other with bilateral adrenal cortical hyperplasia, both showing clinical evidence of Cushing's syndrome, were strikingly different (fig. 1). Both patients showed the presence of the same absorbing substance, although in different concentrations. The absorbing material exhibited a maximum at 235 m $\mu$ . and two inflection points at 228 m $\mu$ . and 242 m $\mu$ . In the patient with adrenal cortical hyperplasia the administration of adrenocorticotropin in the same dosage as that given to the normal individuals caused an increase from values of 2.40 and 2.73 mgm. per diem to 4.64, 5.77, and eventually 6.51 mgm. per diem, with a concomitant disappearance of the inflection at 228 m $\mu$ . When the administration of the hormone was discontinued, the output of absorbing substance decreased to 3.17 and 2.27 mgm. and the inflection at 228 m $\mu$ . reappeared (fig. 2). It thus appears likely that the substance responsible for the inflection at 228 m $\mu$ . is a degradation

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product of the compound which showed a maximum at 235 mu. and an inflection at 242 mu. A comparison of the ultraviolet absorption spectrum (1) reported for  $\Delta^{3,5}$  androstadienone-17 and that found in our patients leaves no doubt as to the identity of the two substances (fig. 2). In the patient with adrenal cortical tumor there was a spontaneous appearance of  $\Delta^{3,5}$  androstadienone-17 in the

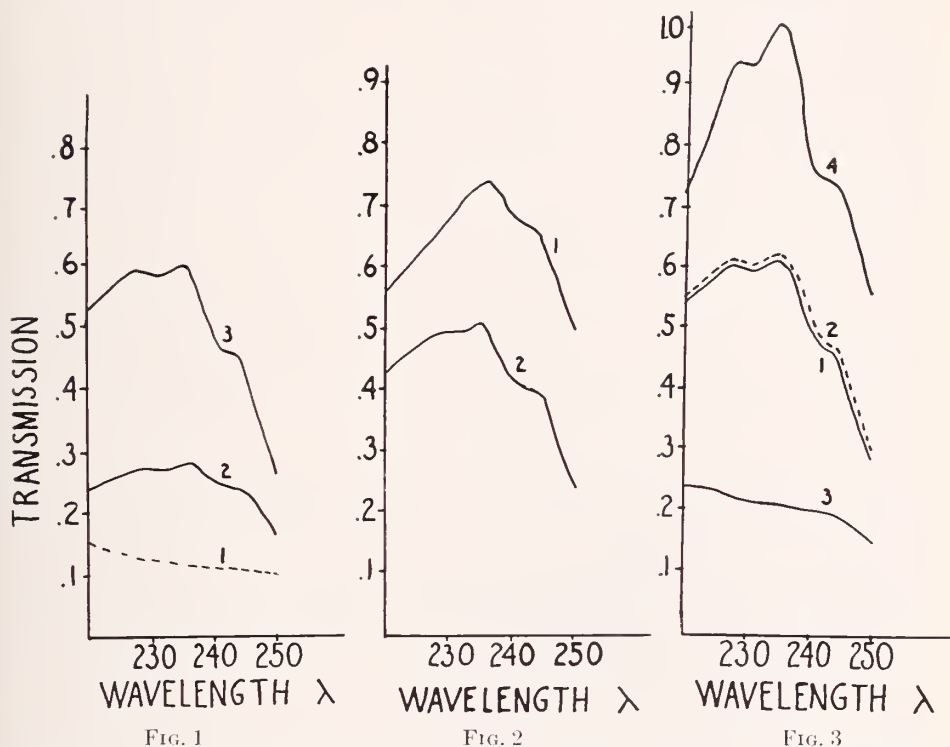


FIG. 1

FIG. 2

FIG. 3

FIG. 1 Ultraviolet absorption curves for ethanol solutions of chloroform extracts; values adjusted to uniform daily output.

(1) Average curve of 15 normal controls.

(2) A case of bilateral adrenal cortical hyperplasia. Average of 4 determinations.

(3) A case of adrenal cortical carcinoma. Average of 6 determinations.

FIG. 2 (1) Urinary excretion of  $\Delta^{3,5}$  androstadienone-17 in a patient with bilateral adrenal cortical hyperplasia receiving injections of adrenocorticotropin.

(2) Three days after discontinuance of injections of adrenocorticotropin in same patient.

FIG. 3 (1) Urinary excretion of  $\Delta^{3,5}$  androstadienone-17 in a patient with an adrenal cortical carcinoma.

(2) During administration of adrenocorticotropin.

(3) Immediately after the surgical removal of the tumor.

(4) One month after operation.

urine. The level of this steroid was 5.26 and 5.93 mgm. per day, almost as high as that observed in the patient with bilateral adrenal cortical hyperplasia following the administration of adrenocorticotrophic hormone. Upon the parenteral administration of adrenocorticotropin to the patient with the adrenal cortical tumor, there occurred no further increase in the level of absorbing substance.

Immediately following the surgical removal of the tumor an examination of the urine failed to reveal more than traces (0.81 mg. per day) of this steroid. A month later the presence of this steroid in the urine reached the preoperative level (5.81 mgm./day) (fig. 3). This reappearance of the steroid coincided with clinical evidence of the development of metastases.

Of interest was the study of two patients with myasthenia gravis with thymic tumors. In one of the patients, on one occasion out of 15 determinations, more than 1 mg. (1.87 mg.) of  $\Delta^{3,5}$  androstadienone-17 was found in the urine. The subsequent administration of adrenocorticotropin to this patient did not result in the appearance of this substance. In the other case, the presence of this steroid in the urine was suggested by the spectroscopic examination, and the parenteral administration of adrenocorticotropin produced a considerable increase in the urinary excretion of this compound.

The only other instance where the urinary excretion of  $\Delta^{3,5}$  androstadienone-17 was elicited in response to the administration of adrenocorticotropin was in the case of a woman with virilizing syndrome associated with diffuse luteinization of the ovaries. In this instance there was no evidence of the presence of this steroid in the urine prior to the administration of adrenocorticotropin.

#### METHOD

A 200 ml. aliquot of a 24 hour sample of urine was brought to pH 1 with concentrated HCl and immediately extracted four times with 100 ml. portions of redistilled chloroform. The 11-hydroxysteroids were then determined in the combined extracts according to the method of Corcoran and Page (5). The following minor modifications were introduced: The final dry residue was dissolved in 3 ml. of acetic acid. One ml. of this was used to determine the 11-hydroxysteroids. Our standard curve was obtained by the determination of formaldehyde obtained from the oxidation of desoxycorticosterone with periodic acid.

The remaining 2 ml. of acetic acid was subjected to a Girard T separation according to Talbot (6). The ketonic extract was evaporated to dryness and the residue redissolved in 5 ml. of redistilled 95% ethanol and again taken to complete dryness. All traces of chloroform were scrupulously removed, after evaporation of the ethanol, by drying the residue for 15 minutes at 50°C and at 1 mm. pressure. This residue was then dissolved in 100 ml. of redistilled 95% ethanol and its absorption spectrum was read in the Beckman spectrophotometer. All solvents were redistilled in an all-glass distilling apparatus.

The percentage transmission readings ( $\log I_0/I$ ) were multiplied by a factor  $\frac{V_n}{V_1}$  in order to render them comparable with the first specimen of the series;  $V_1$  is the daily volume of the first specimen,  $V_n$  that of the sample compared.

The absorption values, as plotted in the figures, correspond to a concentration of the 24 hour steroid output in 600 ml. The actual amount in mgm. of  $\Delta^{3,5}$  androstadienone-17 is computed from these data on the basis of

$$\epsilon_{\max} = 18100 \text{ for } \lambda_{\max} = 236 \text{ mu.}$$

A comparison with a composite absorption curve of 15 normal individuals (Fig. 1, Curve 1) shows the complete absence of any specific absorption at 236 m $\mu$ . and thus excludes the presence of  $\Delta^{3,5}$  androstadienone-17 in quantities of more than 0.1 mg./24 hours. The values in the cases studied were as high as 6.5 mgm./24 hours, which is of a higher order of magnitude than the normal daily output of 11-hydroxysteroids.

#### SUMMARY

1. A method is described for the ultraviolet spectrophotometric identification and quantitative estimation of  $\Delta^{3,5}$  androstadienone-17 in the urine.

2. The appearance of this steroid in the urine of patients with myasthenia gravis with thymic tumors and in the urine of patients with adrenal cortical hyperfunction is described.

3. The influence of the parenteral administration of adrenocorticotropin on the urinary excretion of this compound is discussed.

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# THE ROLE OF ANTIBODIES IN INSULIN RESISTANCE\*

## REPORT OF A CASE

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Within a few years of the discovery of insulin and its use in the management of patients with diabetes mellitus, occasional patients were encountered who required doses that were inordinately large as compared with the average diabetic. These patients were termed "insulin resistant" or "insulin refractory". Their requirement for doses larger than for the ordinary diabetic and larger than the theoretically calculated deficiency due to complete suppression of endogenous insulin production, led to the thought that in these patients the diabetes was on some basis other than insulin lack. Thus it was felt that there were two kinds of diabetics, the one so-called insulin-sensitive, requiring ordinary doses of insulin and presumably due to islet cell deficiency and the other, the so-called insulin-insensitive or resistant, requiring much larger doses and due to some unknown mechanism or factor that in some way counteracted or prevented the physiologic action of insulin.

As a result of recent advances in pancreatic surgery making total pancreatectomy a feasible operation, it has been found by Goldner and Clark (1), Brunschwig et al (2), and Waugh et al (3) that the actual insulin deficiency of the totally pancreatectomized human was not the calculated 200 units per day but rather in the range between 26 and 50. Waugh et al (3) reported a total of nine such cases including four of their own, with a top insulin requirement of only 40 units per day. In view of this work, it is felt that perhaps the concept of insulin resistance should be broadened to include all diabetics who require more than the 50 units per day that the human pancreas apparently manufactures in order to maintain themselves in physiologic equilibrium. According to this broadened definition, a relatively high percentage of diabetics would fall into the category of insulin resistant diabetes, in whom some mechanism beyond pure insulin lack must be postulated. Therefore the attempt to ascertain the exact nature of insulin resistance is more than an effort to explain an occasional aberration where spectacularly high doses are needed and may be basic to an understanding of the pathophysiologic process at work in a very large number of diabetics. Furthermore, even in those patients requiring less than 50 units of insulin per day no definite proof has ever been adduced that the sole underlying pathology is one of insulin lack. In fact, pathologists have long been struck by the paucity of anatomical lesions in the islet cells of the pancreas in diabetic patients and in the lack of correlation between the severity of the diabetic state and anatomic derangements in the pancreas.

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The problem of insulin resistance is, therefore, one of great theoretic interest and practical importance, more than that of explaining the very high needs for insulin (over 200 units per day) in rare patients. The magnitude, however, of the insulin needs in these patients calls for an attempt at elucidation on a larger scale of the phenomena that are perhaps operative in many more patients. Therefore every such case should be studied for whatever light it may throw on this problem, and the following case is one in which the theory of antibody formation as a cause of insulin resistance has been investigated and the literature on this aspect reviewed.

#### CASE REPORT

*History.* A white woman, aged 59 years, (*M. S. H. Adm. #576247*) entered the Mount Sinai Hospital on February 4, 1948 for the fifth time. Some sixteen years earlier (in 1932), she was operated on at another hospital because of symptoms of thyrotoxicosis. She remained well for the following five years. She then noted gradual recurrence of nervousness, excess sudation, weight loss and episodic diarrhea, and in 1943 entered the Mount Sinai Hospital for the first time for further surgical intervention on her thyroid gland. Subtotal thyroidectomy was done and the specimen reported as "hyperplastic thyroid as seen in Graves disease".

Five months later she was readmitted for treatment of a superficial skin infection in the thyroidectomy scar, and two years later, she reentered the hospital for investigation of the origin of some blood that had trickled from her mouth, without antecedent trauma. No bleeding source was found. On all three of these admissions urinalysis was negative for sugar.

Her fourth admission was 2 years later, in 1947, when she was brought to the hospital in a comatose condition. Some six months before this admission she began to lose weight (30 lbs. in 6 months) and complained of weakness, fatigue, and dizziness, and a few weeks before admission she became subject to marked thirst, dryness and sweetness of the mouth, and polyuria. Three days before admission she began to vomit continuously, became drowsy, and her speech was noted to be incoherent. On the day of admission she could not be aroused. The patient was dehydrated, acidotic, and in collapse. A diagnosis of diabetic ketosis and acidosis was established. She was given a total of 2,000 units of insulin in 24 hours; intravenous saline, glucose, alkali, and 5 Gm. of potassium chloride following which she responded rapidly. She was able to leave the hospital on the 11th day taking a daily maintenance dose of 30 units of P.Z.I. each morning.

She was well on this regimen for about 3 months (until January 1948) when she again began to have symptoms of polyuria and polydipsia, and her urine again contained acetone and large quantities of sugar. Her insulin requirement rapidly rose until, at the time of admission, she was taking 160 units of P.Z.I. in the morning with 60 units of regular insulin at the same time, and an additional 60 units of regular insulin with the evening meal. She was readmitted for the fifth time for further study on February 4, 1948 because she was acetonuric even on this regimen and also because of bilateral inguinal adenopathy of a few weeks duration.

*Examination.* The patient was well nourished and well developed giving the impression of being well. Her blood pressure was 108 systolic and 60 diastolic; the pulse, 72; temperature, 98.6°F. The fundi disclosed narrowed arterioles with minimal arterio-venous compression but no hemorrhages or exudates. There was a well healed thyroidectomy scar. The lungs were clear. The heart was slightly enlarged to the left. The liver edge was palpable one finger's breadth below the right costal margin. No other abdominal organs or masses could be felt. Pelvic and rectal examination were essentially normal. There were firm, freely mobile non-tender grape-sized nodes in both groins but no other adenopathy.

There was 1 plus pretibial edema. All peripheral pulses were patent, equal, and syn-

chronous. A neurological examination showed diminished deep tendon reflexes in the upper and absent deep reflexes in the lower extremities. The abdominal reflexes were absent. The posterior column sensations were intact.

*Laboratory data.* Hemoglobin, 12.3 Gm.; red blood cells, 4,000,000; white blood cells, 6,600 with an eosinophilia of three to seven percent. Urinalysis on admission disclosed 3+ sugar, no acetone, trace of albumin. The stool was negative for occult blood, ova and parasites. Sedimentation rate was 38 mm. per hour (Westergren) and repeated before discharge 25 mm. per hour. Blood chemical determinations revealed sugar 226 mg. %,  $\text{CO}_2$  51 vol. %, chloride 544 mg. %, urea nitrogen 8 mg. %, cholesterol 341 mg. %, total protein 7.0 Gms. %, calcium 10.4 mg. %, inorganic phosphorus 2.1 mg. % and alkaline phosphatase 13 King-Armstrong units. Thymol turbidity and cephalin flocculation tests were both negative. Icterus index was 2 and bilirubin 0.2 mg. %. Bromsulfalein test (5 mg. per kilo) showed 11% dye retention after 45 minutes. Blood Wasserman was negative. Studies of the chest X-ray and electrocardiography were normal. Basal metabolic rate on two occasions was +27 and +40, but there was no other clinical evidence of thyrotoxicosis or of any other endocrine dysfunction. Biopsy of one of the slightly enlarged inguinal nodes was reported as "hyperplastic lymphadenitis".

*Course.* At the time of admission, the patient was taking a total of 240 units of insulin daily, on which dosage she had hyperglycemia, heavy glycosuria but no acetonuria or acidosis. She was placed on a diet of C—180, P—100, F—100, a total of 2,000 calories daily, and continued at her usual insulin dosage. It became obvious that this was totally inadequate and her insulin therapy was rapidly adjusted upward as the glycosuria continued unchecked and acetonuria supervened. The largest total dosage in any one day was 900 units and the daily maintenance on which she was finally discharged, and on which she was in satisfactory equilibrium for the greater part of her hospital stay, was 400 units of which 240 units was P.Z.I. and 160 units was regular, given in separate syringes each morning.

At the end of the fourth hospital week, the patient began to manifest allergic reactions to insulin for the first time, with urticaria, induration, redness, and heat at the injection sites relieved partially by pyribenzamine. The patient was tried on various brands of insulin including Squibb's (beef and pork pancreas), Sharpe and Dohme's (beef alone) and Lilly's (mixture of beef, pork, sheep, etc.) as well as special monoantigenic insulins such as Lilly's special pork insulin. There was no consistent pattern, although the patient did react somewhat more to the beef preparations than to the pork and an effort was made to keep her on the pork insulins as much as possible. In any case the reactions were mild, tended to recur with lessening frequency, were controllable with antihistaminics, and were never generalized in scope nor alarming in intensity.

The patient was discharged to the care of her private physician after 45 hospital days on 400 units of insulin daily. At the time of discharge she was free of acetone, spilling less than 1% of sugar in her urine, and free of disturbing allergic reactions. A follow up conversation with her physician ten months after discharge reveals that she is still in an insulin-insensitive state but much less so, taking 120 units per day, in adequate health and without any allergic manifestations.

#### EXPERIMENTAL OBSERVATIONS

Insulin tolerance tests were done in order to demonstrate quantitatively the degree of insulin resistance. The patient, after a night's fast and 24 hours after the last dose of insulin, was given 0.1 unit of insulin per kilo intravenously (method suggested by Goldner (4)). Blood sugars were studied at 0, 10, 20, 30, 45, 60, 90, 120 minutes. According to this method a normally insulin sensitive individual, whether diabetic or not, should show a fall in blood sugar of 50 mg. % or more. As a control patient, another diabetic, who was insulin sensitive, maintained on 10 units of P.Z.I. daily with approximately the same fasting blood sugar, was used. The figures obtained are listed in Table I. It will be seen that the maximum drop in the patient's blood sugar was 35 mg. % as compared with the control which fell 64 mg. %.

Prausnitz-Kustner passive transfer tests were performed in a search for insulin allergic antibodies. Serial dilutions of the patient's serum (undiluted; 1:2; 1:4; 1:8; 1:16;) were injected intracutaneously into 4 recipients in 0.1 cc. quantities. Each of the 4 recipients was injected with the entire series of dilutions. Twenty four hours later 0.1 cc. of U 40 insulin diluted 1:2 (2 units of insulin) was injected into each of the sensitized areas and into control areas. Duplicate series were done on each of the recipients using pork insulin and a mixture of pork and beef insulin. Results were read in 1/2 and in 1 hour. All tests were negative.

Search was made for insulin precipitins in the serum. Two series were done, one using serum undiluted against serial dilutions of the insulin (thus giving test tubes with 20, 10, 5, 2.5, 1.25 units of insulin each in 0.5 cc. of solution and each against 0.5 cc. of serum) and the other series using 0.5 cc. of U 40 insulin (20 units) against 0.5 cc. of serial dilutions of the serum (undiluted; 1:2; 1:4; 1:8; 1:16). These were incubated together in a 37°C. water bath for 2½ hours and then read. They were all negative.

In addition, search was made for insulin neutralizing antibodies using rabbits as the test animal. Stock laboratory animals were used, weighing 3 to 3.6 kilos. They were fasted 24 hours before each series of tests. 4.5 cc of the patient's serum was mixed with 8 units of regular insulin in Series A and 4 units of regular insulin in Series B, each time made up to be a total of 5 cc. These mixtures were injected intravenously into the marginal veins of the rabbits ears, immediately on mixing and after periods of incubation together at 37°C. for 12, 24, 48, and 72 hours before injection. Blood sugars were drawn on the rabbits before

TABLE I  
*Intravenous Insulin Tolerance Test*

	Fasting	10	20	30	45	60	90	120
Insulin resistant patient . . . . .	241	218	206	225	225	205	225	214
Control: insulin sensitive diabetic . . . . .	261	278	214	218	221	214	226	222

Blood sugar determinations in mgs. % after intravenous administration of 0.1 units of insulin per kilo of body weight at time intervals in minutes after the injection of the insulin.

each injection and then serially at ½ hour, 1 hour and 2 hours. A control series was done using the serum of another diabetic patient, not refractory to insulin, maintained on 10 units of P.Z.I. daily and with approximately the same fasting blood sugar. These sera were all drawn from the patients after an all night fast and 24 hours after the last dose of insulin.

The results are tabulated in Table II. As can be seen from the figures, there was no demonstrable inhibitory effect by the serum of the patient on the insulin induced hypoglycemia in the rabbit. There was no difference in the behaviour of the resistant patient and the control. Insulin neutralizing antibodies were not demonstrated by this method.

#### DISCUSSION

Numerous theories have been propounded in an attempt to explain the phenomenon of insulin resistance. Ever since the protein nature of insulin was established the theory of antibody production in response to the antigenic nature of insulin has occurred to many investigators as the possible mechanism of the establishment of insulin resistance. Using various test animals, a mixture of varying quantities of insulin and the serum from resistant patients was injected and the modification of the insulin effect on the blood sugar observed. Review of the literature to date on this subject reveals reports of 30 such pa-

tients (including our own case) with insulin resistant diabetes on whose blood this procedure was performed. Results are listed in Table III.

Of these it can be seen that 20 showed no evidence of insulin neutralizing antibodies by this technique. Of the ten positive results, in only 4 were rabbits used as the experimental animal with serial determinations of the blood sugar (taken from marginal veins in the ear) and in one (24) mice were used with blood sugar determination on the tail blood. The remainder of the positive results were secured with mice or guinea pigs using the less accurate endpoint

TABLE II

*Tests for Neutralizing Antibodies*

Serial Blood Sugars of Rabbits in mgm. % after I.V. Injection of Serum-insulin mixtures

TIME RABBIT BLOOD SAMPLES DRAWN	INCUBATION TIME OF PATIENTS SERUM WITH INSULIN BEFORE RABBIT INJECTION									
	Insulin resistant diabetic					Insulin sensitive diabetic (control)				
	0 hrs.	12 hrs.	24 hrs.	48 hrs.	72 hrs.	0 hrs.	12 hrs.	24 hrs.	48 hrs.	72 hrs.
Before injection . . . . .	96	97	78	103	114	105	145	67	80	113
$\frac{1}{2}$ hr. after inj. . . . .	79	39	35	46	82	61	69	27	34	81
1 hr. after inj. . . . .	42	26	18	48	49	51	68	16*	17	42
2 hrs. after inj. . . . .	34	27	29	—	40	30	25	46	40	30

Series A: 4.5 cc. of patient's serum and 8 units of insulin given intravenously to rabbits.

TIME RABBIT BLOOD SAMPLES DRAWN	INCUBATION TIME OF PATIENTS SERUM WITH INSULIN BEFORE RABBIT INJECTION									
	Insulin resistant diabetic					Insulin sensitive diabetic (control)				
	0 hrs.	12 hrs.	24 hrs.	48 hrs.	72 hrs.	0 hrs.	12 hrs.	24 hrs.	48 hrs.	72 hrs.
Before injection . . . . .	—	99	85	92	91	—	65	112	103	85
$\frac{1}{2}$ hr. after inj. . . . .	—	45	—	48	38	—	47	54	44	64
1 hr. after inj. . . . .	—	—	29	41	60	—	34	47	55	90
2 hrs. after inj. . . . .	—	41	58	51	63	—	48	86	63	90

Series B: 4.5 cc. of patient's serum and 4 units of insulin given intravenously to rabbits.

All rabbits were fasted for 24 hours prior to test.

\* Rabbit convulsed and glueose administered intravenously.

of insulin induced convulsions. Of the 200 negative results on the other hand, 19 were obtained using the more accurate rabbit method with blood sugar determinations.

From these results it is apparent that the preponderance of evidence does not support the contention that the mechanism of insulin resistance is through the development of insulin neutralizing antibodies, capable of inhibiting the normal physiologic response to insulin, although the development of antibodies to the insulin hormone itself has been demonstrated by Wasserman



TABLE III

*Collected Results of Attempts to Demonstrate Insulin Antibodies in Patients with Insulin Resistant Diabetes*

	INSULIN NEUTRALIZING ANTIBODIES	PRECIPITINS	PASSIVE TRANSFER (P-K) TEST	ALLERGIC SKIN TEST	CLINICALLY ALLERGIC
Allan and Constan (5)	Neg.				
Axelrod, Lobe, Ortem, Myers (6)	1) Neg. 2) Neg. 3) Neg.		Neg.	Neg.	No No No
Cannon, Marshall (7)		Pos.	Pos.	Pos.	Yes
Depisch, Hasenohrl (8)	1 out of 4+				
Felder (9)	Pos. (mice)	Neg.	Neg.		No
Fitz (10)	1 out of 3+				
Glass, Spingarn, Pol- lack (11)	Neg.	Neg.	Neg.		No
Glassberg, Somogyi, Taussig (12)	Neg.	Neg.		Neg.	Yes
Glen, Eaton (13)	Pos.				
Goldner, Ricketts (14)*	1/1 neg.	4/7 pos.	4/4 pos.	All 8 pos.	Yes (8)
Karr, Seull, Petty (15, 16)	Neg. Neg.	1:80	Pos.	Pos.	Yes
Lalbe, Boulin (17)	1) ? (G.P.) 2) Pos. (G.P.) 3)	1:200,000 1:800 Neg.	Pos. Pos. Pos.		Yes
Lerman (18, 19)**	4) Pos. (G.P.) 1) Pos. (mice) 2) Pos. (mice)	Neg. ?± Neg.	Pos. Pos. Neg.	Pos.	Yes Yes Slight
Lowell (20, 21, 22, 23, 24)	Neg.				
Lozinski, Frohlich (25)					
Martin, Martin, Lyster, Strouse (26)	Neg.	Neg.	Neg.		Yes
McGavaek, Klotz, Vo- gel, Hart (27)	Neg. (mice)		Pos.		No
Schloss (28)	Neg.				
Schreier (29)	Pos. (mice)				
Strouse, Martin, Mar- tin, Lyster (30)	Pos.				
Taussig (31)	Same patient as Glassberg et al (28)				
Wiener (32)	Neg.		Neg.		No
Our patient	Neg.	Neg.	Neg.		No

\* These authors reported a total of 8 patients with allergy to insulin, but only 3 of whom were insulin resistant. In the 1 of the 3 in whom insulin neutralizing antibodies were looked for, none could be demonstrated.

\*\* Lerman's patient #4 is the same as Lowell's #1, but each is reporting his own studies.

In all cases unless otherwise noted (mice, guinea pigs) the laboratory test animal was the rabbit.

et al (33, 34). These workers have shown that antibodies can develop both against the animal protein carrier and the insulin protein itself but that the insulin antibodies do not impair the physiologic response to insulin, a finding



recently contested by Lowell (35). The antibodies that they demonstrated therefore could not be considered insulin neutralizing antibodies or as insulin anti-hormones in the sense that they antagonize the physiologic action of insulin, and the presence of anti-insulin antibodies in a clinically resistant patient does not by itself establish that the clinical resistance is necessarily due to the presence of antibodies.

Two further discrepancies are apparent in the work among the proponents of the antibody theory as accounting for the clinical phenomenon of insulin resistance. Lowell (22, 23, 24) and Felder (9) both felt that insulin neutralizing antibodies could be demonstrated under optimal conditions after insulin was withheld from the patient and that the failure of others to demonstrate antibodies was due to the fact that previously administered insulin had neutralized what circulating antibodies were present and hence prevented their demonstration in the experimental animal. Glen and Eaton (13) however, found more marked insulin antagonism of the serum, in the rabbit, if the patient had had insulin shortly before drawing the serum. Another fact disturbing to the antibody theory is the finding by Marble et al (36) that the most pronounced alteration of the blood sugar curve was seen not within a few hours of the injection of plasma but rather one to two weeks later. Antibodies carried by passive transfer would be expected to diminish rather than increase in intensity with passage of time.

Closely related to the problem of the existence of neutralizing antibodies has been the problem of allergic antibodies and the two phenomena of resistance and allergy, though oft distinct, have in many instances appeared together (5, 37, 38, 12, 4, 14, 39, 15, 16, 18-24, 26, 40, 29, 41). Some authors (37, 39, 40) have felt that there was a direct causal relationship between the two and that the allergic antibodies were also responsible for the clinical resistance to insulin by tying up the available insulin in antigen antibody reactions, while others (4, 14, 16, 18-24) have presented strong evidence that the two phenomena, while sometimes occurring together, were essentially independent of one another.

Although our patient had minor local allergic reactions to insulin and was therefore one with both allergy and resistance, attempts to demonstrate allergic antibodies by Prausnitz-Kustner passive transfer tests were unsuccessful. Of the 19 patients with insulin resistance (including ours) who had Prausnitz-Kustner tests done (listed in Table III), 12 were also clinically allergic to insulin (see last column Table III) and in 5 no factor of allergy had been present. As one would expect, those with clinical allergic phenomena to insulin showed a higher percentage of positive P-K tests than did those with no apparent insulin allergy. Of the 12 who were clinically allergic to insulin, 9 had positive P-K tests and 3 (including ours) were negative. Of the 5 who were not clinically allergic and had P-K tests done, one still showed allergic antibodies by this test but 4 did not. Our patient fitted in the group with clinical allergy but without demonstrable allergic antibodies by P-K test.

Geldner and Ricketts (14) summarized the preponderant viewpoint on this

question: "Insulin refractoriness is by no means a constant accompaniment of insulin allergy. The majority of patients with allergic symptoms showed no change in their hypoglycemic response to insulin and on the other hand, patients with insulin resistance offer allergic symptoms only occasionally. In general both conditions seem to be independent of each other as well as in the mechanism which causes them." And Lowell (22) "allergy and resistance are independent variables". The great bulk of evidence is in favor of this viewpoint and against the theory that allergy is responsible for resistance.

One other finding of interest, probably closely related to insulin allergy was the mild eosinophilia shown by our patient: up to 7% on one occasion. No other demonstrable cause for eosinophilia could be found. There was no history or clinical evidence of hay fever, asthma, or other atopic disorder. There were no intestinal parasites. Because of the associated inguinal adenopathy, the question of Hodgkin's disease was raised but the negative node biopsy and subsequent regression of the adenopathy dispelled the idea. Eosinophilia as a reaction to insulin itself has been previously reported. Marble (42) found an eosinophilia up to 33% in one patient and Lawrence (43) up to 20% in another. In neither was there any evidence of insulin allergy other than the eosinophilia which was presumed however to be on such a basis. Lawrence and Buckley (44) in a study of 20 non-insulin-resistant diabetics found that 10 of them showed an eosinophilia at one time or another ranging from 4 to 20%, although none had any clinical evidence of allergic reactions to administered insulin. In all of these, other causes of eosinophilia were ruled out by appropriate observations.

Further search for anti-insulin antibodies by the precipitin method was carried out, using serial dilutions of both insulin and of serum in separate series. Our results were all negative. Of the 20 other times that this was carried out in insulin resistant patients (Table III), 8 yielded positive results, 11 negative, and 1 equivocal. From a study of the figures in Table III it can be readily seen that there was no real correlation between the positivity of the precipitin test and the P-K test with the animal protection test. In fact the patient with the highest recorded titer of precipitins (1:200,000) had only equivocal results on the mouse protection test.

Thus it is evident that if the development of antibodies to insulin does play a role in insulin resistance it would account for only a small per cent of the cases.

#### SUMMARY

1. A case of insulin resistant diabetes requiring an average of 400 units of insulin per day in the absence of obvious cause, endocrine, infectious, or otherwise, is described.

2. Search for insulin neutralizing and allergic antibodies in the serum of this patient was negative.

3. From this case and a review of the pertinent literature it is felt that insulin neutralizing or allergic antibodies are not the most probable mechanism in the causation of insulin resistance.

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# HODGKIN'S DISEASE LOCALIZED TO THE ANTERIOR MEDIASTINUM: CLINICAL, ROENTGEN AND SURGICAL CONSIDERATIONS\*

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Hodgkin's Disease is occasionally recognized in a stage in which it is apparently limited to one organ or lymph node group without any clinical or anatomical evidence of the disease elsewhere. At such a stage treatment by surgery, radiotherapy or a combination of both often results in clinical arrest of the disease, in some instances for a period of many years (1). This suggests the possibility that Hodgkin's disease, as a cancer, may arise and spread from a single focus.

A mediastinal mass, consisting of involved lymph nodes, is found in approximately 30-50 per cent of all cases of Hodgkin's disease (2, 3). Reports vary regarding the incidence of peripheral lymph node involvement in the presence of mediastinal Hodgkin's Disease. In a series of 212 cases (4), Goldman did not encounter a single instance of mediastinal involvement without the coexistence of palpable lymph nodes. Kasabach (2) reports that of 77 cases of mediastinal Hodgkin's Disease, 19 were without peripheral lymph node enlargement at the time of the first examination. In Jackson and Parker's series of 90 cases (5) of Hodgkin's Disease with involvement of mediastinal or hilar lymph nodes, there was only one case without peripheral lymph node enlargement. Five instances of Hodgkin's Disease are reported, in which the disease was localized to the anterior mediastinal lymph nodes. The diagnosis, in each case, was established after thoracotomy was performed in an attempt to remove a surgically curable tumor. There was no evidence, clinical or laboratory, that the disease had spread beyond the limits of the anterior mediastinum in any of these cases. Pruritus, splenomegaly, hilar or peripheral lymph node enlargement were absent. One patient (Case #1) complained of intermittent fever for several months prior to admission to the hospital; in three cases (Cases #3, 4, and 5) a mediastinal mass was discovered in a routine survey chest examination and in two cases (Cases #1 and 2) there were symptoms of respiratory involvement.

In Hodgkin's Disease the right paratracheal nodes appear to be affected more frequently than in other conditions causing mediastinal lymph node enlargement (6). The affected mediastinal lymph nodes appear radiographically as a lobulated widening of the mediastinal shadow. Occasionally, the border of the mediastinal shadow is curvilinear. A retrosternal infiltration which is seen on the lateral film of the chest as a scalloped soft tissue mass behind the anterior chest wall has recently been described in Hodgkin's Disease (7). A circumscribed tumor within the anterior mediastinum has not been stressed in the literature as a manifestation of intrathoracic Hodgkin's Disease. Embleton (3) described a case

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in which a large homogeneous, sharply demarcated, right superior anterior mediastinal tumor was proven to be inoperable Hodgkin's Disease. Of 15 operated malignant mediastinal tumors, Blades (9) reported 4 instances of anterior mediastinal Hodgkin's Disease of which 3 were operable; follow-up reports on the course of these patients were not given.

In our cases, the tumors were situated in the anterior mediastinum, superiorly or inferiorly, to the right or left of the midline (figs. 1-6). The tumors were solitary and generally rounded in shape, except for one case (figs. 3 and 4), a right inferior anterior mediastinal tumor, in which a small mass projected from the inferior border of the main tumor. This mass proved to be an additional lymph



FIG. 1



FIG. 2

FIGS. 1 AND 2. Case #4. A large, rounded, left anterior mediastinal tumor diagnosed as a dermoid cyst preoperatively.

node involved in Hodgkin's Disease. The masses were sharply defined with smooth or lobulated contours. All were of homogeneous in density. In one case, however, a left superior anterior mediastinal tumor (figs. 5 and 6) displayed amorphous deposits of calcium at the inferior border. These were not proven to be within the tumor and probably represented calcified pulmonary tuberculosis.

This form of anterior mediastinal Hodgkin's Disease may simulate other anterior mediastinal tumors. Dermoid cysts or teratomas may be differentiated by the presence of calcifications, bony deposits, teeth or an aqueous-lipoid fluid level. Angiocardiography will exclude most aortic aneurysms. The shape of pericardial cysts may alter with respiration. Intrathoracic goiters are frequently calcified and rise on swallowing. All these tumors as well as thymoma, metastatic carcinoma, lipoma and inflammatory lymph node enlargement may radiographically resemble anterior mediastinal Hodgkin's Disease.

Radiosensitivity was not tested preoperatively in these cases, although in

retrospect, a test dose of radiotherapy might have been a diagnostic aid. This procedure generally differentiates malignant lymphoma from other mediastinal tumors. Occasionally, however, a malignant teratoma or thymoma will respond



FIG. 3



FIG. 4

FIGS. 3 AND 4. Case #5. A slightly lobulated, right, inferior anterior mediastinal tumor. The nodule above the right leaf of the diaphragm proved to be an involved lymph node.



FIG. 5



FIG. 6

FIGS. 5 AND 6. Case #1. A lobulated, superior anterior mediastinal tumor. Note calcifications in region of inferior border of mass.

to intermediate dosages of radiotherapy. The diagnosis of Hodgkin's Disease can be made unequivocally only on the basis of the histology of the diseased tissue. For these reasons, one patient (Case #1) was explored despite a history that the mediastinal tumor was found to be radiosensitive 10 years previously.

A thoracotomy was performed in all the cases in this series in an attempt to excise what was believed to be a surgically curable tumor. In two patients (Cases #1 and 2) the tumor was inoperable because of the involvement of the adjacent lung and pericardium. One of these patients (Case #2) died 30 hours postoperatively. In the other cases (Cases #3, 4 and 5) all grossly diseased tissue visible in the mediastinum was removed although the nature of the disease process was not known at the time of operation. Since these three patients were considered to have had a localized type of Hodgkin's Disease and eradication of this form of the disease by either surgery or radiotherapy alone has yielded better than average results, postoperative radiotherapy was withheld in two cases (Cases #2 and 3). Both had mediastinal and cervical recurrences within one and a half years after operation. On the basis of this experience the third patient received radiotherapy to the mediastinum postoperatively. Nevertheless, eight months after operation, an enlarged lymph node appeared in the right axilla. Biopsy proved the node to be the site of Hodgkin's Disease, indicating that the disease was generalized.

#### CASE REPORTS

*Case 1, History.* The patient (J. B. #491255), aged 33, was admitted to The Mount Sinai Hospital on June 17, 1942. Ten years previously, because of cough, fever and loss of weight, an x-ray examination of the chest was made, revealing an anterior mediastinal tumor. Following an unknown dose of radiotherapy the tumor was said to have regressed. An x-ray examination of the chest done in 1935 showed only a prominence in the region of the pulmonary artery. In December of 1948, there appeared cough and retrosternal pressure. X-ray studies at this time revealed the recurrence of an anterior mediastinal mass. On admission, examination disclosed dullness 2 inches to the left of the sternum at the first and second interspaces. The laboratory findings included: Hemoglobin, 75 per cent, white blood cells, 9700 (57 per cent segmented; 8 per cent non-segmented; 26 per cent mononuclear; 6 per cent eosinophiles). Urine, negative, A.Z. test for pregnancy, negative.

X-ray studies of the chest showed a lobulated mass which extended mainly to the left within the anterior superior mediastinum. Irregular calcifications were present at the lower border of the mass. Angiocardiography proved that the mass was not vascular. A diagnosis of teratoid mediastinal tumor was made and an operation was advised but refused. The patient was readmitted about 3 months later (September 14, 1943) because of the recurrence of cough and chest pain. X-ray of the chest showed an appreciable increase in the size of the tumor which now extended to the right as well as the left of the mediastinum. An exploratory thoracotomy was performed on September 21, 1943, and an inoperable tumor was found in the anterior mediastinum infiltrating the left lung, the great vessels, and pericardium. A biopsy of the mediastinal part of this tumor was reported as Hodgkin's Disease. Following the operation, radiotherapy was directed to the mediastinum, H.V.L. 0.9 mm cu., 50 cm. distance, 1500 r (air) to each port in 25 days (estimated tumor dose 1350 r), employing 10 x 15 cm. ports, right and left anterior superior mediastinum and right and left posterior superior mediasti-

num. When the patient was last seen in January 1949 there was no evidence of recurrence, and x-ray of the chest showed only calcifications at the root of the left lung.

*Case 2. History.* The patient, aged 54 years (H. G. #527035), was admitted to The Mount Sinai Hospital on November 5, 1944 complaining of non-productive cough and loss of weight of 2 months' duration. Bronchoscopy done elsewhere, was reported to be negative. Examination on admission disclosed as the only significant abnormality an increased retromanubrial dullness.

The laboratory findings included: Hemoglobin, 61 per cent; white blood cells 16,000 (segmented, 65 per cent; non segmented, 3 per cent; lymphocytes, 25 per cent; mononuclear, 4 per cent; eosinophiles, 3 per cent). Urine, negative.

X-ray examination of the chest showed a rounded, fairly circumscribed mass in the superior anterior mediastinum. Angiocardiography revealed the aorta and pulmonary artery to be normal. The superior vena cava was distorted. A thoracotomy was performed on November 11, 1944 and an inoperable, infiltrating tumor was encountered in the anterior mediastinum; it extended into the hilum of the right lung. The mediastinal portion was biopsied and proved to be Hodgkin's Disease. The patient ceased 30 hours after operation. No post mortem studies were available.

*Case 3. History.* A housewife, aged 29 years (R. E. #55080), was admitted to The Mount Sinai Hospital on October 8, 1946. Her physician informed her in April 1946 that she had a "tumor in her chest". Aside from an occasional wheeze in the left upper chest with slight dullness in this region, there were no significant abnormalities recognizable on physical examination.

Laboratory findings: Hemoglobin, 74 per cent; white blood cells, 14,150 (segmented, 74 per cent; nonsegmented, 3 per cent; lymphocytes, 20 per cent; mononuclear, 3 per cent; eosinophiles, 1 per cent). Urine, faint trace of albumin.

X-ray studies of the chest revealed a rounded, circumscribed left superior anterior mediastinal tumor which measured approximately 8 cm. in diameter. The preoperative diagnosis was mediastinal teratoma. On October 9, 1946, the tumor was resected. It consisted of enlarged lymph nodes affected by Hodgkin's Disease. Since the surgeon believed that all of the diseased tissue had been removed, postoperative radiotherapy was not advised and the patient was discharged on October 22, 1946. The patient was next seen on October 15, 1947 when she was referred to the Tumor Clinic of The Mount Sinai Hospital because of pain and swelling in her right neck for an indefinite duration. She now displayed enlarged lymph nodes on both sides of the neck. X-ray studies of the chest revealed marked enlargement of the hilar, paratracheal and anterior mediastinal lymph nodes. Radiotherapy was then begun (December 19, 1947), and delivered through 2 mediastinal fields, 15 x 15 cm., anterior and posterior, H.V.L. 0.9 mm. cu., 60 cm. distance, 2000 r (air) to each field in 24 days (estimated tumor dose 2200 r) and to the right and left supraclavicular fields, 6 x 8 cm., 2000 r (air) to each field in 22 days. Following treatment, there was marked recession of the cervical and mediastinal nodes. When last seen in March 1949, there was no evidence of recurrence.



*Case 4. History.* A young woman, aged 21 years (E. M. #550185), was admitted to The Mount Sinai Hospital on June 12, 1946. Five months previously a routine x-ray examination revealed an abnormal shadow in the left chest. She complained of occasional mild anterior chest pain and pressure during this period. There were no physical abnormalities except for dullness over the left upper chest anteriorly.

Laboratory findings: Hemoglobin, 81 per cent; white blood cells, 10,400 (segmented, 60 per cent; nonsegmented, 9 per cent; lymphocytes, 23 per cent; mononuclear, 4 per cent; eosinophiles, 3 per cent; basophiles, 1 per cent). Urine, occasional white blood cell, A.Z. test for pregnancy: negative.

X-ray studies of the chest showed a large, rounded, left anterior mediastinal mass. The border of the mass was sharply defined and slightly lobulated. The preoperative diagnosis was dermoid cyst. Left anterior thoracotomy was performed on June 13, 1946. The tumor was resected and it disclosed Hodgkin's Disease. In the surgeon's opinion, all grossly perceptible diseased tissue had been removed and, therefore, post operative radiotherapy was withheld. A chest film taken 10 months later failed to reveal any recurrence. One year postoperatively, however, progressive dyspnea and cough appeared. She was readmitted to the hospital in December 1947. Enlarged lymph nodes were present in the left supraclavicular fossa. X-ray examination revealed a lobulated mass in the left paratracheal region. Radiotherapy was directed to a left supraclavicular port, 6 x 8 cm., H.V.L. 0.9 mm. cu., 60 cm. distance, 3000 r (air) in 35 days (estimated tumor doses: 2800 r) and to 2 mediastinal ports, anterior and posterior, 15 x 15 cm., 2000 r (air) in 36 days. The enlarged mediastinal and cervical lymph nodes disappeared following therapy. The patient was last seen in March 1949 when there was no evidence of recurrence.

*Case 5. History.* A young woman, aged 19 years, a student (R. F. #576299) was admitted to the Tumor Clinic of The Mount Sinai Hospital on January 28, 1948. Two and a half years previously an abnormal mass was found in her right chest on routine x-ray examination. Subsequent x-ray studies revealed a progressive increase in the size of the mass. Aside from occasional sharp anterior chest pain during the previous six months she was virtually asymptomatic. The only significant abnormality found on physical examination was increased dullness to the right of the sternum at the level of the 4th-6th ribs.

*Laboratory Findings:* Hemoglobin, 75 per cent; white blood cells, 6,650 (segmented, 58 per cent; nonsegmented, 8 per cent, lymphocytes, 26 per cent; mononuclear, 5 per cent; eosinophiles, 3 per cent). Urine, negative.

X-ray studies of the chest revealed a rounded mass, with a slightly lobulated border, in the right lower anterior mediastinum. In addition, a small rounded density was present between the lower border of the mass and the anterior portion of the right leaf of the diaphragm. Angiocardiography showed a normal aorta and pulmonary artery. Following a tracer dose of I, 131, profile studies failed to show any radioactivity in the mediastinum. The preoperative diagnosis was thymoma. Right anterior thoracotomy was performed on February 27, 1948. The tumor was excised and histologically it proved to be Hodgkin's Dis-



ease. The surgeon believed that the entire tumor had been removed. However, postoperative radiotherapy was directed to the mediastinum through 2 fields, anterior and posterior, 12 x 18 cm., H.V.L. 0.9 mm cu., 60 cm. distance, 2000 r (air) in 23 days (estimated tumor dose: 2800 r). Follow-up examinations failed to disclose any evidence of recurrence until October 6, 1948 when an enlarged lymph node appeared in the right axilla. The right axilla was treated directly, 2400 r (air) in 15 days. This lymph node regressed under therapy but reappeared in May 1949 when it was excised and showed Hodgkin's Disease.

#### SUMMARY

In this series of five patients with localized anterior mediastinal Hodgkin's Disease, the diagnosis in each instance was established after thoracotomy. Two cases were inoperable. One of these, treated with x-ray, has survived 17 years since the onset with no evidence of disease at present. In three cases, all gross evidence of disease was excised at operation. Surgery was not curative in these cases, since recurrence of disease appeared within a year and a half postoperatively. It is believed survey x-ray studies of the chest will reveal such instances of mediastinal Hodgkin's Disease more frequently.

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# HEMANGIOMA OF THE PONS<sup>1</sup>

## CASE REPORT AND REVIEW OF THE LITERATURE

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Hemangioma of the pons is rare, judging from the number of cases reported since Virchow originally described a vascular tumor of the pons in 1851 (1). Only 23 such instances, verified by autopsy, could be found recorded in the literature. In 19 of these, the pontine lesion was discovered at postmortem examination; there were no clinical manifestations suggesting the nature or location of the lesion. In one of the remaining 4 cases, a murmur was heard over the skull and an intracranial hemangioma was suspected; its location, however, remained obscure. In the other 3 cases, a pontine tumor was diagnosed, but in none was it identified as an angioma. The same is true of the following case.

### CASE REPORT

*History.* R. Z. (Adm. #576924; P.M. #13925) was observed at The Mount Sinai Hospital on 4 different occasions. He was first admitted September 8, 1943, at the age of 4 years. His main complaint was difficulty in speech of 4 months' duration. Until the development of this disturbance he had been apparently well, aside from an inconsequential head injury a year earlier. In the family history, it was noted that both grandparents died of "cancer." His older brother died 8 years previously following an operation for hydrocephalus at another hospital; there were no angiomas at postmortem.

Four months prior to admission, following a series of upper respiratory infections, his tonsils were removed. Immediately after the operation, his speech took on a nasal quality and thereafter continued progressively to deteriorate. He dropped consonants, particularly L's and R's, and was thought to have difficulty in selecting the correct words. (It was discovered later that he merely failed to use the words he could not pronounce clearly; no true aphasia was present.) At about the same time it was observed that his left eye did not follow objects to the left. With this he appeared generally weak and became tired easily. One day before admission, he was found to be dragging his right foot on walking.

*Examination.* The child held his head tilted to the right. His speech had a nasal quality and he substituted other words for those with several consonants, which he could pronounce only with difficulty. A left facial paralysis of central type<sup>2</sup> was present. The left external rectus oculi was completely paralyzed. The soft palate was weak on voluntary movement, but showed an exaggerated excursion following reflex stimulation. The tongue deviated to the right when protruded. There was a slight but definite weakness of the extremities on the right side, and he tended to fall to the right when walking. The deep reflexes were generally increased, more so on the right. The right lower abdominal reflex could not be elicited. Babinski and Hoffman signs were present on the right.

*Laboratory data.* The urine and blood count were normal. A blood Wassermann test was negative. Lumbar puncture yielded clear, colorless fluid under normal pressure; it contained 28 mg. per cent of protein; Pandy, Wassermann and colloidal gold reactions were negative. Electroencephalography showed a moderate amount of diffuse and almost symmetrical delta activity, with frequencies as low as 4 per second and amplitudes up to 120

<sup>1</sup> From the Department of Laboratories, Division of Neuropathology, The Mount Sinai Hospital, New York.

<sup>2</sup> In view of later developments, it is possible that this observation was incorrect.

microvolts; there was no focal accentuation. A pneumoencephalogram was done and revealed a widening of the pons and a dorsal convexity of the floor of the 4th ventricle (fig. 1). Plain x-ray films of the skull and chest were normal.

*Course.* During the first month of observation at the hospital, sustained right ankle clonus and complete loss of movement of the soft palate appeared.

A glioma of the pons was considered the most likely possibility. Radiotherapy to this area was begun, discontinued when the patient contracted chicken pox, but resumed following recovery from this intercurrent malady. He left the hospital November 21, 1943, but continued to receive radiotherapy as an out patient.

An unanticipated and marked improvement occurred in the course of the next 5 months. At this time (March, 1944)<sup>3</sup> radiation was discontinued and it was observed that the patient was walking without difficulty, the right arm and leg had almost completely recovered nor-



FIG. 1. Pneumoencephalogram, showing the backward displacement and dorsal curve of the floor of the 4th ventricle. The distance from the dorsum sellae to the floor of the 4th ventricle was found to be 4.2 cm. (normal maximum in the adult, 4 cm.).

mal power, the left abducens paralysis had disappeared, and there was no dysphonia. His condition remained unchanged for the next year.

*Second admission* (May 22, 1945). Symptoms reappeared abruptly 4 days prior to admission. He began to complain of mild, generalized headache and 2 days later of pain over the right eye. He was unable to sit up, complained of dizziness, and found it difficult to sleep. The next day his speech became noticeably slower, his head tilted to the right and his left hand appeared to be weak.

On admission, there was some clouding of consciousness. His neck was slightly rigid and the head was held tilted and rotated toward the right. Tonic neck reflexes could not be elicited. The extraocular movements were impaired, as shown in Figure 2. The entire left side of the face was paralyzed. There was a total bilateral palatal paralysis. He was unable to speak or swallow and could protrude his tongue only slightly. There was almost

<sup>3</sup> He received a total of 2400 r (in air) to each of 3 portals: right lateral pons, left lateral pons, and direct occipital.

complete paralysis of the left (*sic*) upper and lower extremities, with only a flicker of voluntary movement. The left abdominal reflexes were absent and there was a bilateral Babinski sign. Lengthening and shortening reflexes could be demonstrated in all 4 extremities. There seemed to be some decomposition of voluntary movement, but tests of cerebellar function were difficult to interpret because of poor cooperation.

It was felt that transection of the brain stem was taking place and x-ray treatment was started immediately. On the third day in the hospital, the patient developed signs of acute respiratory distress, radiation was discontinued, and he was treated with oxygen, suction, aminophyllin and penicillin. As his pulmonary symptoms abated, radiotherapy was resumed. This was followed by gradual improvement: at the termination of radiation treatment, June 13, 1945,<sup>4</sup> he was able to move his left arm and leg very well, the dysphagia and dysphonia had disappeared and he was able to walk without assistance.

He remained reasonably well for about 6 months. Signs of bulbar involvement recurred at the end of that time and, in spite of another course of radiotherapy,<sup>5</sup> became progressively severe.

*Third admission.* The advance of bulbar signs culminated in an acute episode of cough, fever and dyspnea September 10, 1947, and 3 days later he again entered the hospital.

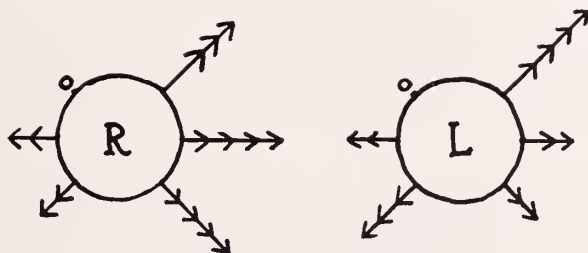


FIG. 2. Schematic representation of the ocular movements. The length of the arrows is proportional to the extent of excursion.

The lungs were filled with moist rales. There was a high fever and the patient was severely dyspneic. Neurological examination showed, in addition to the abnormalities noted on the previous admission, coarse vertical nystagmus, dysdiadochokinesis, loss of cheek reflexes, and a return of the severe dysphonia and dysphagia.

A diagnosis of aspiration pneumonia was made, and the patient responded to treatment with oxygen and penicillin. Radiotherapy<sup>6</sup> did not influence the neurological manifestations, however. He was discharged October 25, 1947, for terminal care at home, where his condition became steadily worse.

*Fourth admission.* The child was brought to the hospital for the last time February 20, 1948. He was comatose and areflexic, with rapid, irregular respirations and an almost imperceptible pulse. The pupils were dilated and fixed to light. He died one hour after arriving in the reception ward.

*Postmortem findings. Gross.* The autopsy was limited to the head. There were no abnormalities in the scalp, calvaria or meninges. The brain weighed 1260 Gm. There were

<sup>4</sup> Between May 25 and June 13, 1945, a total of 1800 r (in air) was given to each of the lateral portals mentioned previously.

<sup>5</sup> Starting in December, 1945, each of the 3 previously mentioned areas was treated with 1100 r. An additional 1100 r was administered to a superior occipital portal (all doses in air).

<sup>6</sup> From September 17 to October 10, 1947, the right portal received 900 r, the left 750 r, and the direct occipital 825 r (in air).



occasional, well-defined, hemorrhagic spots, each about the size of a pinhead, on the surfaces of the cerebral hemispheres, without any other alterations.

The *pons* was swollen and soft, the reduced consistency extending into the adjacent right brachium pontis and upper part of the medulla oblongata. All the affected structures were somewhat discolored, having a dirty yellow appearance. The vessels at the base of the brain, particularly the vertebral arteries, exhibited prominent, firm, yellow atheromatous plaques. Sections of the pons and the medulla oblongata showed many hemorrhagic nodules, replacing almost all of the normal markings of the pons at the level of the trigeminal nuclei, except for a small area in the basis pontis (fig. 3A, B and C). The floor of the 4th ventricle was elevated by some of the tumor nodules, which were deep red in color. The hemorrhagic discoloration extended caudally into the upper part of the medulla oblongata and rostrally through the entire length of the midbrain (fig. 3D) into the left thalamus. The tumor nodules were sharply separated from the surrounding, partly intact, brain tissue;

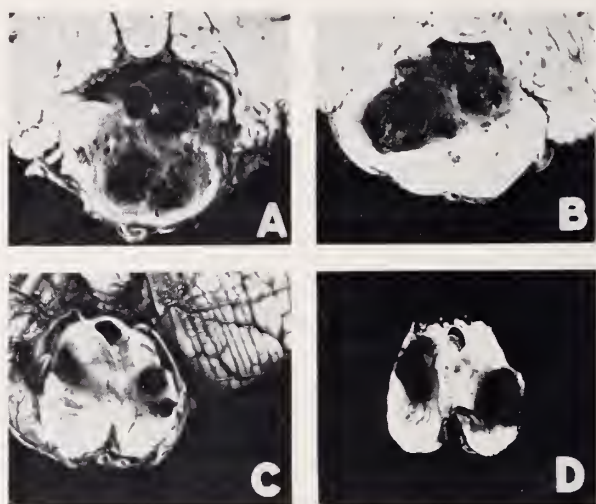


FIG. 3. Cross sections of the brain stem (natural size). A. Medulla oblongata, showing large angiomatic vessels, with surrounding brownish discoloration and hemorrhage. B. Pons, at the level of the trigeminal nuclei. The tegmentum is almost completely replaced by the tumor. C. Pons, upper part. One large angiomatic vessel is present; the other two areas, with less sharply defined borders, are hemorrhages. D. Midbrain. Only hemorrhages are seen; there is no angiomatic tissue present at this level.

they alternated with less distinct areas of discoloration, which characterized all the lesions in the midbrain and thalamus.

*Microscopic observations.* The discrete nodules in the pons and medulla oblongata were found to consist of many anomalous blood vessels, varying in size. Some of them had ruptured and were surrounded by fresh blood in the neighboring brain substance. The walls of the vessels varied greatly in thickness: some of them had the character of sinusoids, enclosed by one or two thin layers of endothelium and connective tissue, while others were thick-walled channels resembling arteries and veins (fig. 4). The walls of the latter were composed of dense fibrous connective tissue, with occasional fragments of muscularis and elastica. A few vessels of capillary size were present, their walls almost completely calcified (fig. 5). Calcareous deposits were also present in the walls of some of the larger channels, appearing as irregular, linear streaks. Blood, apparently recently exuded, was found enveloping the sinusoids; in some places an actual dissection of the wall had taken place, with the endothelial layers split and blood appearing both between these layers and outside





FIG. 4. The adjacent walls of two angiomatous vessels. The thick, densely calcified upper wall contrasts with that of the lower channel, although the latter contains much more blood. (Hematoxylin and eosin stain;  $\times 150$ .)

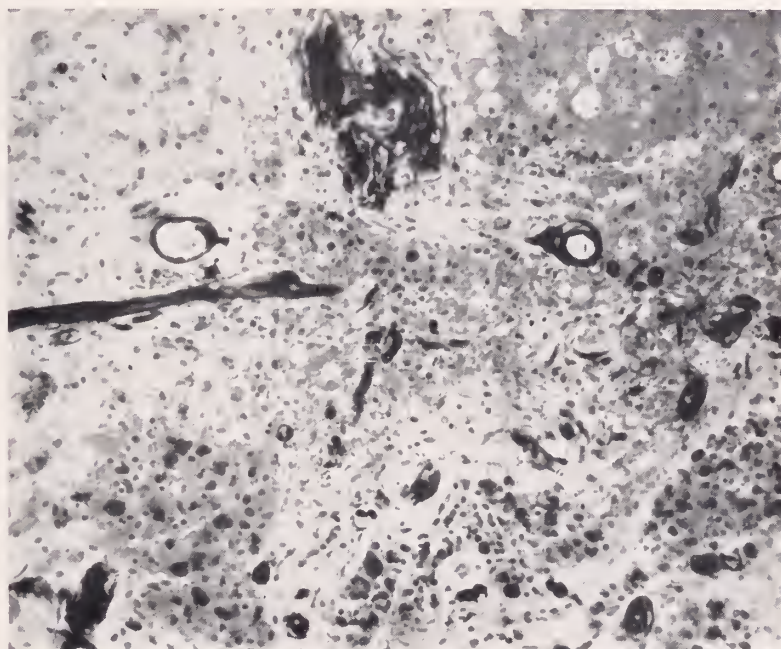


FIG. 5. Small, calcified vessels in the vicinity of the angioma. (Hematoxylin and eosin stain;  $\times 200$ .)

the vessel. Blood from the ruptured vessels in the pons and the medulla oblongata diffused through the midbrain and extended into the thalamus. Both these structures disclosed no abnormal vessels and were involved only secondarily by this recent hemorrhage.

The nervous tissue intervening between the neoplastic vascular formations was rarefied and displayed gliosis. In the immediate vicinity of the angiomatous channels the nerve cells exhibited a variety of regressive changes: they were compressed and displaced, with their long axes in the direction of the vessel walls; the nuclei were swollen or fragmented; in many cells there was a striking vacuolization of the cytoplasm; the Nissl substance was clumped and displaced, or altogether lost; many of the nerve cells were filled with hemosiderin. Numerous large macrophages, within the brain substance and in the walls of the larger neoplastic vessels; also contained large amounts of hematogenous pigment.

Within the cortex of the cerebral hemispheres, the pinhead-sized lesions noted grossly showed only thin-walled, dilated channels of moderate size, surrounded by a narrow zone of cerebral rarefaction and gliosis.

*Comment.* Throughout the clinical course, the signs and symptoms were considered to point to a tumor in the pons. The crossed hemiplegia, the marked involvement of the lower six cranial nerves (singly and in pairs), and the pneumoencephalographic findings (fig. 1) confirmed this impression. In the interpretation of the air encephalogram in this case, it was found that the distance between the clearly defined posterior wall of the cisterna pontis and the floor of the 4th ventricle was 3.6 cm., and from the dorsum sellae to the floor of the 4th ventricle, 4.2 cm. These measurements are outside the normal range, even for adults [average 2.8 cm., and from 3.3 to 4 cm., respectively (22)], and gave proof of a space-occupying lesion of the pons. The dorsal convexity of the floor of the 4th ventricle demonstrated in this case is also typical.

The sequence of events, characterized by recurrent acute episodes of bulbar paralysis regressing on radiotherapy early in the disease, might be regarded as suggestive of hemangioma. Although neuroectodermal tumors sometimes respond to radiotherapy, such gratifying results as were obtained in this instance are rarely seen except in angiomas. Glioma of the pons, for example, was recorded as a final diagnosis in 20 patients at The Mount Sinai Hospital during the past 15 years (including 10 verified and 10 unverified cases). Of the total of 20, 13 patients received radiotherapy. Of these, some improvement was reported in 6, whereas in the remaining 7 this treatment was apparently ineffective. In no case was any more than slight improvement recorded, and in several cases even that much was not agreed upon by all those who saw the patient. Further more, the average survival period of the irradiated cases (19 months) was essentially the same as for those in which no radiotherapy was given (21 months).

Considering the pathological findings in this case, attention may be drawn to the evidence of recurrent hemorrhage, which can be held responsible for the acute exacerbations of symptoms. The presence of nerve cells laden with hematogenous pigment supports this contention; it is a common finding in angiomas, and by some (9) considered as typical. In one part of the medulla oblongata there was a group of almost completely calcified small vessels among the larger angiomatous channels (fig. 5). Such formations are said to be found in some brains which have been subjected to large amounts of radiation—in the course

of 5 years, this patient received about 17,500 r (in air; tumor dose, 9250 r) to the brain stem area—but it is equally common in both the blood vessels actually involved in angiomas and those supplying and draining them, as a manifestation of degenerative processes. They were confined to only one area in all the sections studied, however, and the blood vessels of the cerebellum, although exposed to the same radiation as the brain stem, showed no abnormality. It is probable, therefore, that the calcification was related to the basic lesion and not to the radiotherapy. The atheromatous changes in the basal vessels, striking in a patient this age, were probably not caused by radiotherapy, for the same reasons.

#### DISCUSSION

An analysis of the cases of angioma of the pons recorded in the literature, summarized in the accompanying tables, reveals the fact that the disease presents no pathognomonic symptoms or signs.

In only 5 of the 24 cases was the pontine lesion associated with definite clinical evidence of its presence (table I). Of the remaining 19 cases, 10 were totally incidental postmortem findings and had no relation to the patient's illness (table II). In another 4 cases, the tumor in the pons may or may not have had some bearing on the ultimate outcome of the disease, but there were no localizing or identifying signs during the clinical course (table III). The remaining 5 were incompletely described and hence do not lend themselves to analysis (table IV).

In 9 cases, the lesion in the pons was part of a more or less widespread angiomatosis of the brain and spinal cord. In one it was associated with a glioma in the 4th ventricle and Alzheimer's senile plaques in the cerebral cortex.

The ages of the patients ranged from 8 to 81 years and the duration of the assumed clinical course also varied widely, from one day to as long as 25 years. The clinical features in all the cases gave no real clue as to the underlying disease process. In the 4 cases in which there was a reasonable suspicion of a pontine tumor (table I), the angiomatous nature of the lesion was not recognized. The reverse, however, was true in the case of Richardson and Bagnall (5), where the presence of a bruit and a history of recurrent subarachnoid hemorrhage gave a substantial lead that an angioma was present. Unfortunately, it was not until shortly before death that signs appeared which could have been regarded as significant of brain stem involvement.

A large assortment of names was employed to designate the character of this pathologic process, among them cavernous angioma, telangiectasis, capillary angioma, sinusoid angioma, hemangioma arteriale racemosum, naevus angiomatosus, arterial angioma and cystic angioma. The nomenclature of blood vessel tumors, particularly those of the brain, is by no means uniform and it is obvious that some of these names represent varying interpretations of terminology, rather than basic anatomical differences. Although in recent years the classification proposed by Cushing and Bailey (17) has been generally followed, it has not been accepted in its entirety, as many modifications of their scheme have been suggested since the monograph was published (24, 25, 26, 27, 28).

As in the case of any classification, however, there are instances among tumors in which a definite assignment to a specific category is difficult or impossible.

TABLE I

*Definite signs and symptoms of a pontine tumor, or features suggesting angioma*

CASE OF	SEX	AGE AT DEATH	CLINICAL FEATURES	DURATION	PATHOLOGIC FINDINGS	ANGIOMA ELSEWHERE IN CNS
Leyser (2), (1922)	♀	20	Crossed (abducens and facial) hemiplegia	20 days	Small angioma (tel-angiectasis) in pons	0
Jentzer (3), (1938)	♂	57	Progressive bulbar palsy (Nn. VII, IX, XI, XII bilaterally)	3 mos.	Large angioma (cystic) of medulla oblongata, extending into pons	+
Zeldenrust (4), (1938)	♀	29	Sudden onset of diplopia, headache, bulbar palsy	3 days	Multiple angiomas of brain; single large ruptured sinusoid in pons	+
Richardson & Bagnall (5), (1940)	♂	23	Recurrent subarachnoid hemorrhage between ages 7 and 12, with full recovery. Sudden subarachnoid hemorrhage with left hemiplegia and signs of decerebration. Bruit over skull	?16 yrs.	Signs of old and recent hemorrhage in pons and vermis cerebelli, surrounding arterial angioma.* Shrunken right cerebellar hemisphere	+
Present case	♂	8	Recurrent bulbar paralysis with crossed hemiplegia; good initial response to radiation, then no effect	5 yrs.	Large angioma (ruptured) of pons and medulla oblongata, with extension of hemorrhage into midbrain and thalamus. Tiny angiomas in cerebral hemispheres	+

\* In view of the clinical findings and the uncertain status of arterial angioma (most investigators believe that an entirely arterial angioma does not exist), it is not unlikely that the lesion in this case was actually an arteriovenous angioma (aneurysm).

Wolf and Brock (23) emphasized this problem with respect to cerebral angiomas. For example, the demonstration of the functional connections of vessels essential for proving the existence of an arteriovenous angioma can not be made



TABLE II

*The pontine angioma was an incidental postmortem finding. Signs and symptoms were caused by an unrelated lesion*

CASE OF	SEX	AGE AT DEATH	CLINICAL FEATURES	DURATION	PATHOLOGIC FINDINGS	AN- GIOMA ELSE- WHERE IN CNS
Virchow (1) (1851)	♀	Adult	Spontaneous abortion. Short period of delirium before death	Few days	Hemorrhagic spot in pons (telangiectasis). Liver angiomas	0
Creite (6) (1903)	♀	21	Jacksonian convulsion (left hand) at age 2. No intervening symptoms. Short episode of status epilepticus	? 19 yrs.	Multiple cerebral angiomas (cavernous) in cerebral hemispheres cerebellum and pons	+
Nambu (7) (1907)	♂	63	Sudden onset of coma	Hours	Chronic Bright's disease, cirrhosis of liver. Small angioma (cavernous) of pons	0
Enders (8) (1908)	♀	60	Long - standing diabetes, with 24 hours of convulsions (eyes turned to right), mental confusion, continuous clonic spasms of entire right side. Died in a few hours	1 day	Very small angioma (hemangioma arteriale racemosum) in pons	0
Claude & Loyez (9) (1911)	♂	68	Fall (without loss of consciousness) followed by right hemiplegia. No change for 2 months then sudden coma	2 mos.	Small pontine angioma (capillary angiectases) and vascular dilatation in spinal cord	+
Lafora (10), (1911)	♂	63	Psychosis; no localizing signs. Coma and death in 6 days	6 days	Angioma of basis pontis, small ependymoglioma in 4th ventricle and Alzheimer's plaques in cerebral cortex	0
Lafora (11), (1912)	♀	22	Psychosis, fever, productive cough. Generalized convulsions without loss of consciousness. Status epilepticus	Few mos.	Dilated vessels in pons. Suppurative pulmonary disease (?tuberculosis)	0



TABLE II—*Continued*

CASE OF	SEX	AGE AT DEATH	CLINICAL FEATURES	DURATION	PATHOLOGIC FINDINGS	AN- GIOMA ELSE- WHERE IN CNS
Sommerfelt (12) (1919)	♀	57	Diabetes; no neuro- logical findings	Not stated	Several masses (naevi angiomatosi) in pons	0
Kufs (13),* (1928)	♂	81	"Senile dementia;" sudden death	Few yrs.	Small angioma (cavernous) in pons; multiple angiomas of skin and brain	+
Sjövall & Lundgren (14) (1938)	♂	56	Jacksonian convulsions (right leg), right hemiplegia. Died in marked hyperthermia	15 days	Ruptured angiomas of cerebrum. Small, unruptured angiomas (telangiectases) in basis and tegmentum pontis	+

\* The daughter of Kufs' patient, aged 17 years, had a sudden onset of crossed (abducens and facial) hemiplegia. The author assumed that she also had a pontine angioma, but pathological examination was lacking.

by mere morphologic studies of postmortem material. The tumor herein described, because of the great variety of vascular formations within it, was classified under the general term *hemangioma*, as any more specific definition was found unjustifiable.

As already indicated, the clinical recognition of pontine angiomas is very difficult and this diagnosis is not often considered. Some light may be thrown on this problem, however, if the cause of the clinical manifestations in cerebral angiomas in general is investigated. Cushing and Bailey (17) reviewed this subject in 1928, and although little has been added since then to clarify the problem, much has been written. Briefly, the theories are these:

1. *Hemorrhage*. This is a common occurrence and is the most frequent demonstrable cause of symptoms. It is, of course, particularly serious in the brain stem. It was undoubtedly the precipitating factor in our case, as there was good evidence of both old and recent hemorrhage in the affected brain stem structures. The abrupt onset of symptoms and the known widespread hemorrhage just before death strengthen this impression.

2. *Edema*. Increased vascular permeability in association with infection or trauma would be expected to affect tissues in angiomatous areas as well as around normal blood vessels. The greater amount of vascular tissue, however, and the well known degenerative changes that take place in these vessels lead to greater transudation. Lafora (11) in his own case proposed that intercurrent disease produced the additional insult, in the form of edema, to cause death. This explanation may have to be accepted in the absence of any hemorrhage, which is often the case. The time relationship, in our case, between the first symptoms

TABLE III

*The role of the pontine angioma in the clinical course of the patient is uncertain*

CASE OF	SEX	AGE AT DEATH	CLINICAL FEATURES	DURATION	PATHOLOGIC FINDINGS	AN- GIOMA ELSE- WHERE IN CNS
Clingenstein (15), (1908)	♂	50	Epilepsy, believed idiopathic, 25 years. Attacks more frequent in 3 months before death. Died suddenly in a convulsion	? 25 yrs.	Angioma (ruptured) in upper pons	0
Malamud (16), (1925)	♀	39	Headache, diplopia, vertigo, mental changes. Diagnosis of multiple sclerosis	Few mos.	Multiple cerebral angiomas (cavernous), one in midline of pons	+
Cushing & Bailey (17), (1928)	♀	33	Attacks of prolonged unconsciousness; negative suboccipital exploration. Almost well for 8 years, then sudden coma	8 yrs.	Small angioma (telangiectasis) in lower pons	0
Courville (18) (1937)	♂	70	Mental confusion, dizzy spells. Diabetes. Died of strangulated femoral hernia	18 mos.	Large angioma, (cavernous) in left side of basis pontis	0

TABLE IV

*Insufficient data were given to permit any clinicopathologic correlation*

CASE OF	SEX	AGE AT DEATH	CLINICAL FEATURES	DURATION	PATHOLOGIC FINDINGS	AN- GIOMA ELSE- WHERE IN CNS
Schley (19)* (1928) Case 1 Case 2 Case 3 Case 4					Capillary angioma Capillary angioma Capillary angioma Cavernous angioma	
Bergstrand, Olivecrona & Tönnis (20) (1936)	♀	32	Progressive nervous symptoms"	1 yr.	Large angioma (telangiectasis) of pons	0

\* In Schley's report, only these data were given.

Note: The case of Wirgman (21), cited in Courville's review (18), was not included in this analysis. It represented a cystic cerebellar hemangioma which extended for a short distance into the middle cerebellar peduncle.

and tonsillectomy gives rise to such speculation. Edema and hemorrhage in lesions of this type are, in the last analysis, only different stages in the same basic process, that is, weakening of the vascular walls.

3. *New growth.* The view is held by most investigators that angiomas are capable of neoplastic expansion. Of the reported cases of angioma of the pons, it is likely that this was a precipitating cause of symptoms in only one instance (Jentzer (3), table I), where a "cystic angioma," probably hemangioendotheliomatous, caused progressive encroachment on the structures of the medulla oblongata and pons. Expansion in such tumors may not be entirely neoplastic, however, as transudation into cystic angiomas or progressive engorgement of the vessels in others might produce the steady advance of symptoms not unlike that found in new growths.

4. *Thrombosis.* This is common in angiomas. The abnormal vessels, however, by virtue of their large size, thick walls and the stagnation of blood which occurs, contribute little to the nutrition of the tissue and thrombosis is of little importance.

5. *Engorgement.* Simple distention of the existing vascular channels, with transient compression of the surrounding structures, may give rise to symptoms.

6. *Arteriovenous angiomas.* The "by-passing" of the capillary bed that characterizes this type of lesion anywhere in the body produces a certain degree of anoxia of the neighboring tissue. Some investigators (23) feel that these lesions may be entirely venous at first, and that they later acquire arterial connections. Were this change to occur rapidly, the sudden "arteriolization," with elimination of the capillary vessels in this area, might lead to abrupt symptoms.

The foregoing theories, it must be emphasized, are largely theoretical. The actual determination of the course of pathologic events in a given case is often impossible.

#### SUMMARY

1. A case is described in which a pontine tumor was present in a boy aged 4 years. The clinical course, over a period of 5 years, was marked by recurrent attacks of bulbar palsy, responding to radiotherapy. Pathologic studies revealed a large hemangioma involving the pons and medulla oblongata, with recent massive hemorrhage from the tumor extending through the midbrain into the left thalamus.

2. The rarity of angioma of the pons is emphasized. The few recorded cases are analyzed clinically and pathologically.

I wish to express my sincere appreciation to Dr. Joseph H. Globus for his careful supervision and kind encouragement in the preparation of this paper.

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## INSPIRATORY INCREASE OF THE PULSE AMPLITUDE, ITS RELATION TO PULSUS PARADOXUS<sup>1</sup>

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The phenomenon of marked inspiratory decrease in the amplitude of the radial pulse associated with regular heart action was first described in adhesive pericarditis by Williams (1) in 1850. Kussmaul (2) noted the same phenomenon in a patient with mediastino-pericarditis and called it *pulsus paradoxus*. This term unfortunately may be interpreted to mean that inspiratory decrease is abnormal and that in normal persons there exists an inspiratory increase in the amplitude of the pulse. Cabot and Adams (3), Norris and Landis (4), and Fishberg (5) remark that "pulsus paradoxus" or inspiratory decrease in the pulse amplitude may be seen occasionally in normals and is at times related to pressure on the subclavian artery by the first rib and the clavicle. Levine (6) gives a similar explanation for the occurrence of a decreased to absent radial pulse upon inspiration in normal individuals. White (7) in the third edition of "Heart Disease" states that "the paradoxical pulse consists of marked decrease of the systolic and pulse pressures, even to the point of obliteration, during inspiration, in contrast to the usual and normal increase of the pulse during inspiration in the case of diaphragmatic breathing". The writings of these authors may have given the impression that an inspiratory decrease in the pulse amplitude is paradoxical. Such is not the case. Inspiratory decrease in the pulse amplitude is not paradoxical and is the normal phenomenon in thoracic breathing. This much clouded issue was elucidated by Lewis (8) in his classical studies on the relation of respiration to blood pressure. It was his opinion that "Kussmaul's pulse is a pulse which diminishes in tension during deep inspiration, and is the normal event in the vast majority of subjects, healthy or diseased". He also stated that "as a physical sign it is almost worthless, and that the impression of its constitution as implied in the term paradoxical is entirely erroneous". van der Mandele (9) in his monograph, also contributed to the elucidation of pulsus paradoxus. Heinbecker (10) shortly thereafter again demonstrated in normals an immediate fall in the systemic arterial pressure on inspiration and an immediate rise on expiration. Since then a great deal of physiological research has been done in an attempt to explain completely this phenomenon.

Inspiratory increase in the amplitude of the pulse due to mechanical compression of the innominate artery during expiration was reported by Hay (11) in a case of aneurysm of the aortic arch. Hay called this phenomenon "reversed pulsus paradoxus". Ortner (12) also reported an inspiratory increase of the pulse amplitude in a case of aortic aneurysm involving the innominate artery. This increase

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was relative because the basic alteration was an expiratory decrease in the pulse amplitude. More important, the normal inspiratory decrease of the pulse amplitude was noted on the uninvolved left side. This normal inspiratory decrease was explained by the pooling of blood in the lungs during inspiration with reduction in left ventricular output. The inspiratory decrease in left ventricular output in turn reduced the size of the aneurysm and relieved the mechanical pressure on the ostium of the innominate artery, thereby increasing the pulse amplitude on the involved right side. On the basis of these observations, Ortner, like Lewis, felt that *pulsus paradoxus* was a misnomer.

It is the purpose of this communication (a) to report by graphic methods some further observations on inspiratory increase of the pulse amplitude noted in some cases, in certain pathological conditions, namely, patent ductus arteriosus, interatrial septal defect with pulmonic stenosis, tetralogy of Fallot, Eisenmenger complex and congestive heart failure; (b) to review the effect of respiration on the normal pulmonary and systemic circulation; and (c) to attempt to explain this dynamic type of inspiratory increase in pulse amplitude in light of known physiological relationships. Although these observations are few in number, they are interesting enough to be reported at this time in order to stimulate further investigation of the subject. Our cases of inspiratory increase in the pulse amplitude differ from those of Hay and Ortner in that mechanical compression related to respiration is absent.

#### METHOD AND MATERIAL

The method of investigation consisted of graphically recording the amplitude of the radial pulse with a gelatin-filled rubber capsule attached to a tri-beam electrocardiograph (Sanborn). The patient was requested to take a deep breath and simultaneous tracings of the radial pulse with deep inspiration and expiration were recorded. No graphic record was made of the type of respiration i.e. abdominal and/or thoracic. Inspiration in each instance was initiated by a verbal command from the observer. It was therefore assumed that inspiration was predominantly thoracic (Lewis (8)). The patients investigated were those in whom an inspiratory increase of the radial pulse was already suspected on clinical grounds.

The amplitude of the pulse was measured on the tracing from the base line at the onset of the ejection phase to the peak of the flow phase.

#### CLINICAL OBSERVATIONS

*Normal:* In 79 normal persons, there was an inspiratory decrease of the amplitude of the pulse (fig. 1). The immediate increase in rate cannot be considered a sinus arrhythmia. It is secondary to the fall in blood pressure (Lewis (8)).

*Patent Ductus Arteriosus: Case M. S. (MSH #582069)* a white man, aged 29 years, with patent ductus arteriosus proved by surgical operation. Fig. 2A reveals inspiratory increase in pulse amplitude prior to operation. Fig. 2B demonstrates the change to normal inspiratory decrease following successful ligation of the ductus.

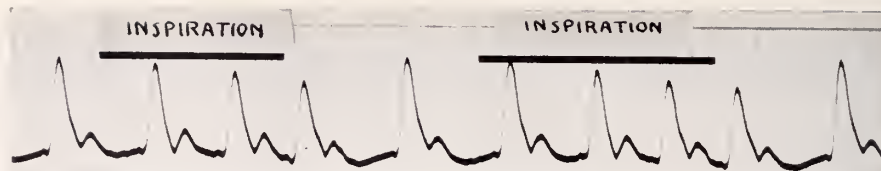


FIG. 1. Radial pulse tracing of a normal 32 year old male. Note the inspiratory decrease in the pulse amplitude—the normal event. The slight increase in rate is secondary to the fall in blood pressure.

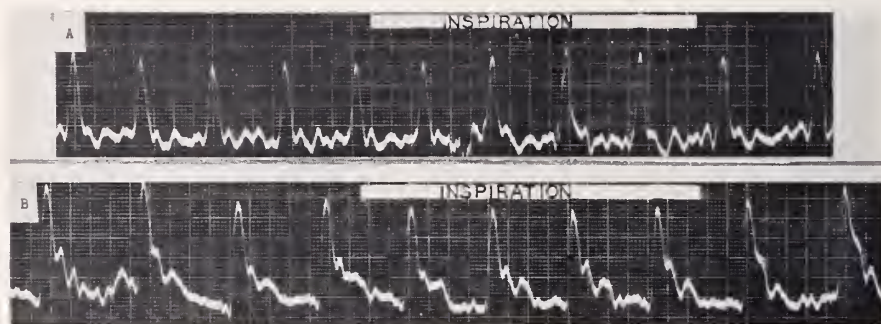


FIG. 2. Patent Ductus Arteriosus. A—Before operation. Inspiratory increase in the pulse amplitude. B—After successful ligation. Note change to inspiratory decrease.

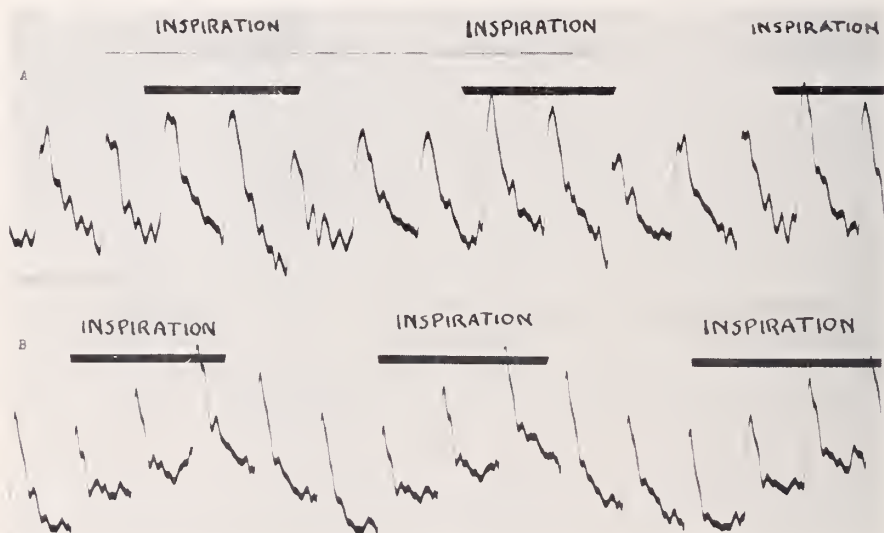


FIG. 3. Patent Ductus Arteriosus. A—Before operation. Note inspiratory increase in amplitude of pulse. B—Unsuccessful attempt at ligation. Inspiratory increase still present.

*Case G. B. (MSH #579663)* a white female, aged 48 years, with a diagnosis of patent ductus arteriosus established by angiocardiography and microplethysmography. Fig. 3A taken preoperatively reveals an inspiratory increase in the

pulse amplitude. At operation a widely patent ductus arteriosus and an aneurysmal dilatation of the pulmonary artery was found. Complete ligation was impossible. Fig. 3B after unsuccessful operation still reveals the inspiratory increase in pulse amplitude.

*Case R. S. (MSH #582075)* a white female, aged 20 years, with patent ductus proved by surgical operation. Fig. 4 a preoperative record demonstrates inspiratory increase in pulse amplitude. No post-operative record was taken.

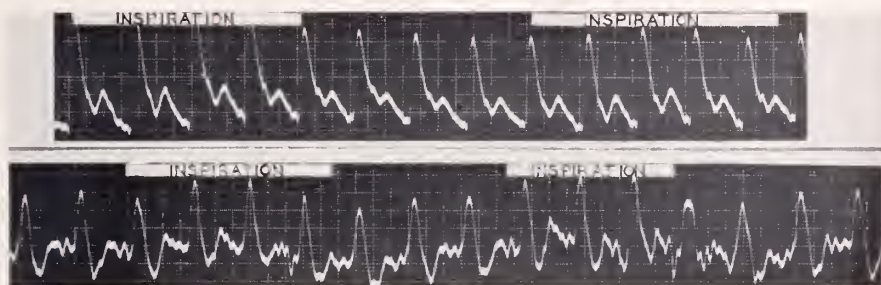


FIG. 4. (*Upper*) Patent Ductus Arteriosus. Pre-operative tracing shows inspiratory increase in amplitude of the pulse. No post-operative tracing taken.

FIG. 5. (*Lower*) Interatrial Septal Defect with Pulmonic Stenosis. Inspiratory increase in the pulse amplitude.

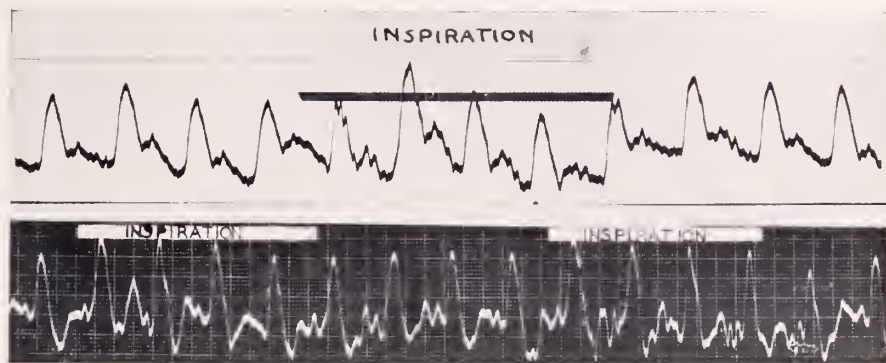


FIG. 6. (*Upper*) Eisenmenger's Complex. Inspiratory increase in the pulse amplitude

FIG. 7. (*Lower*) Tetralogy of Fallot. Inspiratory increase in the pulse amplitude

*Interatrial Septal Defect with Pulmonic Stenosis: Case M. D. (MSH #580482)* a white female, aged 29 years, with a diagnosis of interatrial septal defect and pulmonic stenosis proved by angiocardiography. Fig. 5 reveals inspiratory increase in pulse amplitude.

*Eisenmenger Complex: Case S. G. (MSH #582782)* a white female, aged 18 years, with Eisenmenger's complex proved by angiocardiography. Fig. 6. reveals inspiratory increase in the pulse amplitude.

*Tetralogy of Fallot: Case G. S. (MSH #593643)* a white female, aged 30 years,



with tetralogy of Fallot proved by angiocardiology and operation. Fig. 7 reveals inspiratory increase in the pulse amplitude.

*Heart Failure: Case M. J. (MSH #576847)* a white female, aged 61 years, with arteriosclerotic heart disease, constrictive pericarditis and severe heart failure proved by autopsy. Fig. 8 reveals inspiratory increase in pulse amplitude.

*Case N. S. (MSH #585612)* a colored female, aged 47 years, with thyrotoxicosis and rheumatic heart disease with mitral stenosis and insufficiency, in severe heart failure. Fig. 9 reveals inspiratory increase in pulse amplitude.

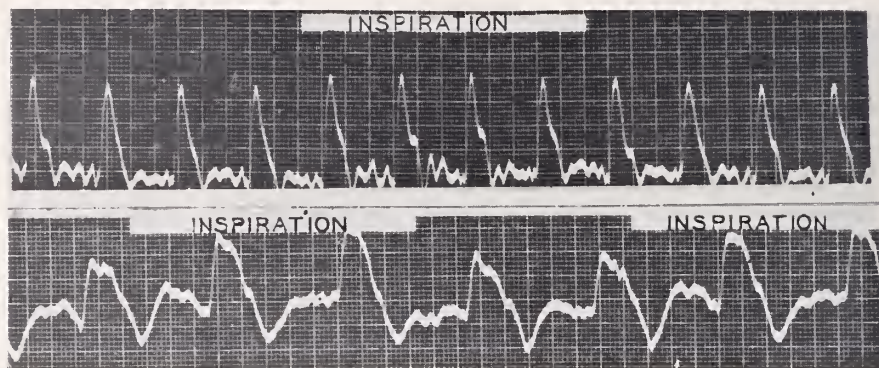


FIG. 8. (*Upper*) Arteriosclerotic Heart Disease with Constrictive Pericarditis in Failure. Inspiratory increase in the pulse amplitude.

FIG. 9. (*Lower*) Thyrotoxicosis, Rheumatic Heart Disease with Mitral Stenosis and Insufficiency. Heart Failure. Inspiratory increase in pulse amplitude.

#### DISCUSSION

For a more complete understanding and explanation of the phenomenon of inspiratory increase in the pulse amplitude it seems worth while at this time to review briefly the effect of respiration on the normal pulmonary and systemic circulation.

However, before this may be done, certain facts must be made clear. Purely abdominal breathing and purely thoracic breathing produce opposite effects. With abdominal breathing, there is a rise in blood pressure on inspiration; with thoracic breathing, there is a fall in blood pressure on inspiration. Artificial respiration gives a rise of blood pressure during inspiration and a fall during expiration. It is well to note, as pointed out by Lewis (8) that the response of a patient to the request, "take a deep breath", produces in men and women in the great majority of instances a deep thoracic inspiration. The generally accepted view that men breathe with the abdomen and women with the thorax does not affect the question. We are dealing with a voluntary act. Therefore, since all the patients in this series were studied under such conditions, when we refer to "inspiration", thoracic inspiration is supposed.

A more detailed discussion on the effects of respiration on blood pressure will be found in the writings of Lewis (8), van der Mandele (9), Ortnier (12), and Courmand and his associates (13).

The following events take place during deep inspiration and are reversed during expiration.

1. *Increase in Right Atrial Filling:* The greater negativity of the intrathoracic pressure during inspiration increases the capacity of the intrathoracic great veins and the right heart chambers (14). The right atrium enlarges and atrial filling increases.

2. *Increase in the Pressure in the Right Atrium:* This occurs at the end of diastole of the atrium (15, 16) due to the increased filling of this chamber associated with the greater negative intrathoracic pressure.

3. *Increase in the Diastolic Filling of the Right Ventricle:* The combined diastolic volume and stroke volume of the two ventricles are augmented with inspiration, especially when the inspiration is deep and prolonged. This was first shown by Boyd and Patras (17). These authors did not explain, however, why the systemic pressure should decrease during inspiration. It remained for Shuler and associates (18) to demonstrate that the inspiratory dilatation of the heart in diastole is due entirely to an increase in the size of the right ventricle, the left ventricle actually decreasing in size. This work was done on dogs with a portion of the ventral chest wall removed, exposing the heart. Paper markers were used to outline each ventricle; motion pictures were taken through a sealed-in-window. The right ventricle showed increased diastolic size and stroke volume during inspiration, while the left ventricular size and stroke volume decreased. It was pointed out that each ventricle responded independently of the other, regardless of the diastolic size of the individual ventricles.

4. *Increase in the Right Ventricular Stroke Volume and Minute Output:* Due to the increased inspiratory filling of the right ventricle, an increased stroke volume and minute output from this chamber occurs in accordance with Starling's principle (19).

5. *Increase in the Pulmonary Artery Pressure* (20, 21): Due to the increase in the right ventricular stroke volume and minute output, the pressure in the pulmonary artery rises.

6. *Increase in the Blood Holding Capacity of the Pulmonary Vessels:* That the pulmonary vascular bed can change in its capacity has been known for some time. The evidence to date points to the fact that the capacity of the pulmonary vessels normally increases during inspiration to an extent more than sufficient to absorb the increase in the right ventricular output (12, 22, 23, 24, 25, 26, 27). As a result an increment of blood is pooled in the pulmonary vascular bed, this increment being withheld from the left ventricle. The thin-walled pulmonary veins act as the main pooling area.

7. *Decrease in Left Ventricular Filling:* Because of the pooling of blood in the pulmonary vascular bed during inspiration a diminished return of blood to the left side of the heart results. Left ventricular filling is therefore decreased.

8. *Decrease in the Left Ventricular Stroke Volume and Minute Output:* This is a direct result of the decrease in left ventricular filling.

9. *Fall in Aortic Pressure:* Two factors play a role here: (a) the direct but minor effect of the increased negativity of the intrathoracic pressure on the aorta



(28) and (b) the indirect but major effect of a decrease in the left ventricular output.

In the final analysis, the development of a normal inspiratory decrease in the pulse amplitude will depend upon the relationship between the right ventricular systolic output on the one hand and the capacity of the pulmonary bed on the other hand. The greater the capacity of the pulmonary bed, the larger will be the increment of blood withheld from the left ventricle during inspiration and conversely, the smaller the capacity of the pulmonary bed, the smaller will be the increment of blood withheld from the left ventricle during inspiration.

By this reasoning it was inferred that if the pulmonary bed were saturated, the increased stroke volume of the right ventricle on inspiration might be transmitted directly to the left ventricle producing an increase in the systemic pulse amplitude during inspiration,—a condition contrary to the normal. In addition it was felt that if there were a shunt of blood from right to left greater than the increment of stroke volume withheld by the pulmonary bed, an inspiratory rise might again be expected. It was also reasoned that if the increased output of the right ventricle were shunted directly to the aorta without the intervening pulmonary bed (as seen in certain types of congenital heart disease with over-riding of the aorta), again an inspiratory increase of the pulse amplitude might be observed. This investigation was performed in order to test the validity of these hypotheses.

Changes in the vascular capacity or elasticity of the pulmonary bed may be seen in various disease states such as patent ductus arteriosus, congestive heart failure, and pulmonary fibrosis. In cardiac insufficiency the pulmonary bed is saturated because of left ventricular failure. In patent ductus arteriosus the large continuous shunt from the aorta to the pulmonary artery may produce the same effect. In pulmonary fibrosis the vascular bed is diminished and unable to expand. Presumably in these conditions only a small increment of blood can be withheld from the left ventricle by an already overloaded, inelastic pulmonary bed. As a result the increase in the right ventricular output which normally occurs during inspiration would then be transmitted directly to the left ventricle and therefore the left ventricular filling, the left ventricular stroke volume and aortic pressure would rise. Thus an inspiratory increase in the pulse amplitude would occur. This is noted to occur in patent ductus arteriosus as shown in Figures 2, 3 and 4. Figures 8 and 9 are tracings obtained in two patients with severe congestive heart failure. These were the only cases in a selected series of twenty patients with severe heart failure in which this phenomenon was observed. Investigation of many cases of pulmonary fibrosis and emphysema has failed as yet to produce the inspiratory increase predicted on theoretic grounds. It may be significant however, that many of these cases showed no inspiratory decrease. This might be explained by the fact that these patients have a limited vital capacity and are unable to inspire deeply enough.

In the patient with interatrial septal defect and pulmonic stenosis (fig. 5), as a result of the hemodynamics of pulmonic stenosis there is a shunt of blood from the right auricle to the left auricle during inspiration over and above the increment withheld by the pulmonary bed. This would then increase the left ventricu-

lar filling and left ventricular stroke volume. The aortic pressure would rise and finally this would be reflected as an increase in the pulse amplitude.

In the Eisenmenger complex and tetralogy of Fallot (figs. 6 and 7) the aorta stems partially from the right ventricle and an inspiratory increase might be expected. In this condition, the normal inspiratory increase of right ventricular filling and stroke volume is transmitted directly to the aorta, eliminating the damping effect of the pulmonary bed.

The clinical importance of inspiratory increase in the pulse amplitude has not been determined by our limited observations. All conditions have not been investigated nor have statistical studies been done on those investigated. In some of the conditions in which inspiratory increase of the pulse amplitude was found, it was possible to note a difference by palpation of the radial pulse while the patient drew a deep breath. In other instances pulse tracings were necessary. In heart failure the phenomenon occurs but is uncommon. Its significance in congenital heart disease will not be determined until a more extensive study has been done, although it is easy to conceive that it might be useful clinically in the differential diagnosis of some lesions.

In a series of 79 normal individuals, we have not observed inspiratory increase in pulse amplitude.

Other factors, both normal and pathological, may influence the relationship between respiration and circulatory dynamics producing the classical "pulsus paradoxus" of Kussmaul. A marked decrease in pulse amplitude may be seen in normal athletes, laryngeal stenosis or compression, intrathoracic mediastinal tumors, scalenus anticus syndrome, and cervical rib syndromes. Classically it is found in pericardial effusions and constrictive pericarditis. A complete discussion of this phenomenon may be found in the writings of van der Mandele (9), Ortner (12), Gauchat and Katz (29), Wennekebach and Winterberg (30), and Hitzig (31). Suffice it to say that the marked inspiratory decrease in pulse amplitude even to the point of obliteration (classical pulsus paradoxus) is merely an accentuation of the normal, whereas inspiratory increase in pulse amplitude in our series of cases has always been associated with cardiovascular disease.

#### CONCLUSIONS

1. Inspiratory increase in the amplitude of the pulse is reported in 3 cases of patent ductus arteriosus, 1 case of interatrial septal defect with pulmonic stenosis, 1 case of the Eisenmenger complex, 1 case of tetralogy of Fallot and in 2 cases of severe heart failure.

2. Increase in the amplitude of the pulse with a deep voluntary inspiration was not observed in normal individuals. No studies on abdominal breathing were made.

3. The term "pulsus paradoxus" in common use today is confusing. Inspiratory decrease of the pulse is a normal event.

4. The effect of respiration on the pulmonary and systemic circulation is reviewed and an attempt is made to explain inspiratory increase in the pulse amplitude in light of known physiological relationships.

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## RESTORED VIABILITY OF IMPLANTED PRESERVED NECROCARTILAGE IN RHINOPLASTY\*

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The clinical use of cadaveric cartilage has become extensive especially in the past twelve years, due to the excellent contribution of O'Connor and Pierce (1, 2). Because of its accessibility and availability, facility in storage, manipulation and modelling, preserved necrocartilage has many advocates. The great advantage of necrocartilage is the relatively insignificant price paid by the recipient for camouflage or support of a nasal deformity, with elimination of a potentially hazardous operation of rib resection.

Many enthusiastic supporters of this method have reported a high percentage of takes. Hoyt de Kleine (3), for example, following the technique recommended by Pierce and O'Connor, reported 100 implants of preserved cartilage in the past seven and one half years. Of these, only four were unsuccessful due to absorption or extrusion. Straith and Slaughter (4), reviewing one hundred consecutive cases in which necrocartilage grafts were employed, reported success in ninety four per cent of the operations.

On the other hand, there are many like Brown (5) who object to necrocartilage because it is not resistant to infection and can be completely absorbed even without infection. His statement, based upon observations over an eleven year period, emphasizes that "Undoubtedly there is a reaction around these transplants that in many instances will result in complete solution of the graft. It is definite that absorption takes place to some extent in all instances and that complete loss may occur by a gradual process without visible reaction over a period of several months."

Peer (6) also stresses the unreliability of preserved isogenous cartilage. His experimental work demonstrated that preserved cartilage over a long period is invaded and replaced by fibrous tissue. For nine months the isogenous cartilage graft is tolerated as a foreign body; it then goes through a gradual process of invasion by the surrounding tissue with slow absorption. This may take two years.

In view of these contradictory opinions and paucity of histological reports of preserved necrocartilage removed from a nose after a good take in nasal reconstruction, the following report may be of significance. It indicates a metaplasia to viability by the necrocartilage as a result of the response of the surrounding host's tissue.

### CASE REPORT

The patient, a woman aged 35 years, had undergone several rhinoplastic procedures by various surgeons. The first operation was followed by a saddle de-

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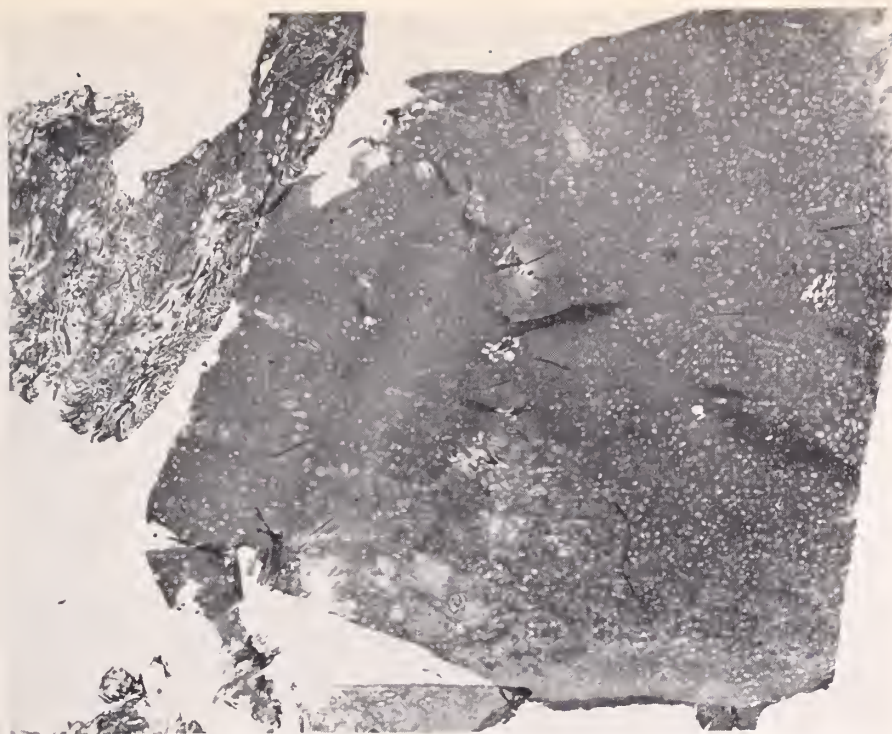


FIG. 1. Photomicrograph of the piece of necrocartilage which had been transplanted in nose 3 years prior to its removal. It shows fibrous tissue adherent to the cartilage. (Low power magnification).

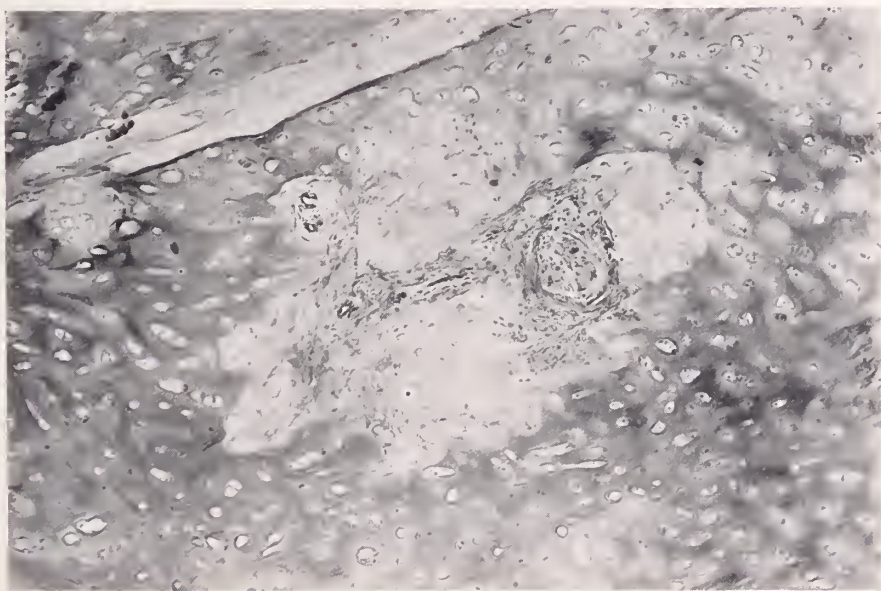


FIG. 2. Photomicrograph of the piece of necrocartilage illustrated in Figure 1. It shows vascularized cartilage in the centre and cartilage cell which appear to be viable. (High power magnification).

formity. One year later a bone graft taken from her ilium was inserted in the nose to correct the saddle. Evidently the result of this graft was not satisfactory. In November of 1945 she was again operated upon, the bone graft was removed and replaced by a refrigerated rib isograft. The patient was still dissatisfied and came to the Rhinoplasty clinic for opinion and correction if advisable. The revision was performed in December of 1948. The preserved rib cartilage was removed. It was observed during the process of freeing the graft, that it was unusually firm in its attachment to the surrounding tissues, especially in its caudal half, so that on removal a considerable amount of surrounding adherent fibrous tissue came with the graft.

The graft was sent to the pathology laboratory for microscopic examination. This was reported as follows: "vascularized cartilage with adjacent connective tissue, fat and muscle without significant change." The pathologist was unaware that the tissue was necrocartilage (figs. 1 and 2).

#### CONCLUSION

A case is reported in which preserved cadaveric rib cartilage which had been inserted in a nose three years previously underwent metaplasia *in situ* with concomitant histological features typical of viable cartilage.

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## ABSTRACTS

### AUTHORS' ABSTRACTS OF PAPERS PUBLISHED ELSEWHERE BY MEMBERS OF THE MOUNT SINAI HOSPITAL STAFF

Members of the hospital staff and the out patient department of the Mount Sinai Hospital are invited to submit for publication in this column brief abstracts of their articles appearing in other journals.

*Kernicterus. A Review with a Report of the Findings in a Study of Seven Cases.* P. VOGEL AND P. F. L. BECKER. J. Neuropath. & Exper. Neurol., 7: 190, April, 1948.

Seven cases of kernicterus are described, all associated with erythroblastosis fetalis, confirmed by means of serologic and histologic studies. In 5 cases the infants were Rh positive and the mother Rh negative with anti Rh antibodies. In one case the erythroblastosis was presumably due to the A factor, and in another case the erythroblastosis was due to the Rh' factor. Slow movements of the extremities, suggestive of choreo-athetoid movements, were recorded in 1 case. In 5 cases, jaundice appeared during the first day of life; postmortem studies disclosed the discoloration to be present most frequently in the following structures: hippocampus, basal ganglia, midbrain, medulla and floor of the fourth ventricle. The microscopic findings, except for the 6 and 7 cases, were uniform. In regions grossly bile-stained the nerve cells were shrunken and stained readily with eosin, some containing dark staining nuclei. Some nerve cells displayed poorly stained cytoplasm and vacuolization. These alterations are not improbably the result of venostasis. No alterations of the glia cells, microglia, or connective tissues were detected. In 2 cases there was yellow pigment present in scattered nerve cells in the hippocampus, basal ganglia, pons, cerebellum (Purkinje cells) and medulla oblongata (olives). Perivascular aggregations of undifferentiated neuro-epithelial cells were found scattered in their usual distribution. Extramedullary erythropoiesis, chiefly in the liver and spleen and visceral hemorrhages were other anatomical findings.

*The Course of Beriberi Heart Disease in American Prisoners-of-War in Japan.*

R. J. ALLERMAN AND G. H. STOLLERMAN. Ann. Int. Med., 28: 949, May, 1948.

The modern clinical concept of Beriberi heart disease emphasizes the variable course and manifestations of this syndrome and broadens the criteria for its diagnosis beyond the earlier-described classical features. A history of nutritional deficiency in a case of chronic heart failure without other apparent etiological factors may be sufficient to suggest the diagnosis of beriberi heart disease. Two cases are presented in detail from a group of patients who were American prisoners-of-war in Japan and who suffered from advanced and protracted beriberi. The contrasting courses of these cases confirm the experimental evidence which emphasizes factors of physical exertion, increased carbohydrate consumption and partial thiamin deficiency in the production of beriberi heart and illustrate the importance of prolonged rest, careful observation and intensive therapy in the management of this condition. The first case also illustrates that in its advanced stages beriberi heart disease may simulate other types of chronic myocardial insufficiency.

*The Pathogenesis of Splenomegaly in Hypertension of the Portal Circulation; "Congestive Splenomegaly".* E. MOSCHOWITZ. Medicine, 27: 187, May, 1948.

A morphological study of 86 spleens in various maladies associated with hypertension of the portal circulation was made. The finer morphology of these spleens was studied from



the biological point of view, and the changes were traced from the earliest to the most mature phase. This investigation was aided by the simultaneous study of an accessory spleen in a few cases. The evolution is identical whatever the cause of the portal hypertension. The morphological difference is merely one of degree. Other things being equal, the more distal the obstruction from the hilus of the spleen, the less intense the lesions. The duration of the portal hypertension is a much greater factor in increasing the intensity of the lesions than the height of the pressure. The morbid histology is modified by exsanguination, an associated infection or cardiac failure. Reasons have been submitted for believing that portal hypertension is the only factor that produces these lesions. The lesions in the spleen are interpreted as a venocapillary sclerosis. In the terminal stages of the morbid process, the circulation of the spleen is thus converted from an open to an almost closed one. This seriously compromises the reservoir function of the organ. Teleologically, the venocapillary sclerosis may be viewed as a compensatory adaptation to the increased intravenous pressure. Megakaryocytes and extramedullary hematopoiesis only occur in the terminal stages and are usually simultaneous reactions. They probably represent a phylogenetic reversion. There are, no "unknown causes" for "congestive splenomegaly" when cases can be submitted to post mortem study. The term "congestive splenomegaly" is not strictly accurate, because congestion and venous hypertension are not necessarily synonymous phenomena.

*Urological Complications of Regional Ileitis.* LEON GINZBURG AND GORDON D. OPPENHEIMER. *J. Urol.*, 59: 948, May, 1948.

Urological symptoms and signs develop in about 4 per cent of patients with regional ileitis. Bladder symptoms are due to an inflammatory process which varies in severity from a mild extra-vesical inflammation to a large peri-vesical abscess or even an ileo-vesical fistula. Another group of patients present a retroperitoneal abscess simulating a perinephric abscess. X-ray studies of the small bowel lead to the correct diagnosis. After primary disease of the urinary tract has been excluded, surgical treatment is indicated. Ileocolostomy with division of the ileum will cure the intestinal disease and its urological complication.

*Curare (Intocostrin) in the Acute State of Anterior Poliomyelitis.* D. ROSENBERG AND A. E. FISCHER. *Pediatrics*, 1: 648, May, 1948.

The efficacy of curare was tested during an epidemic of acute anterior poliomyelitis. Previous reports indicated that prompt relief of pain and decrease of spasm were to be expected. When the physical therapists who were treating our patients found little or no relaxation in the affected muscles, and the goniometric measurements showed no evidence of improvement when the drug was used in doses previously recommended, the dose was cautiously increased in some patients. Larger amounts were tolerated with safety by some. Others, however, reacted alarmingly to small doses. This difference in therapeutic response may be explained by individual variations in response to a drug or by the fact that the concentration of the drug may rise rapidly, sometimes to unpredictable heights, before falling (Schlesinger). The dangers of giving curare to patients with bulbar involvement, especially to those in which there is beginning bulbar or intercostal muscle weakness are pointed out; also the probable cumulative effect when injections are given less than 8 hours apart. The beneficial effects of small doses of curare, with which the authors obtained little or no muscle relaxation in the acute stage cannot be confirmed or denied, when such doses are given for weeks in combination with physical therapy.

*The Mechanism of Adhesive Plaster Irritation.* S. M. PECK, H. ROSENFELD, K. K. LI, AND A. GICK. *J. Invest. Dermat.*, 10: 367, May, 1948.

There are three types of irritation due to adhesive tape: A relatively unimportant fleeting reaction which is most marked in hairy areas and is due to the mechanical trauma of removing the tape. This is the more marked, the more the tape adheres to the skin. A

reaction due to specific sensitivity to one or more of the ingredients of the adhesive tape. This is relatively rare. A reaction due to changes in pH, and to the bacterial flora on the skin surface under the adhesive plaster. This is the most common type. Bacteriostatic and bactericidal agents such as fatty acid salts incorporated in adhesive plaster, can play an important role in preventing this reaction by depressing the bacterial flora. Our experiments indicate that the bacteria of the skin surface play a role in the irritation produced by adhesive tape. The incorporation of bactericidal and bacteriostatic agents tends to eliminate the type of adhesive tape irritation in which the bacteria play a role. It could be shown that when the irritation was due to bacteria, it could be prevented by previous treatment of the skin with the fatty acid salts. The irritation could not be prevented if it was due to specific sensitization to ingredients of the adhesive plaster.

*It Takes Training to Be a Good Trustee.* J. TURNER. Med. Hosp., 70: 96, May, 1948.

This article is a letter written to the Vice-President of the MODERN HOSPITAL, the editor of which asked permission to publish part of it as a short article. The title was supplied by the editor. The points made are: (a) Doctors have an important contribution to make to the management of a hospital and there should be a mechanism to obtain this contribution adequately and fully. (b) The controlling board of a hospital must be a wholly disinterested body; doctors should not be on the board although they are indispensable in an advisory capacity. (c) Membership on Boards of Trustees is no longer limited to men of wealth and social position. The base is being broadened as other talents and abilities are being recognized and drawn in. (d) Finding a competent hospital administrator is not an easy task. The necessary training and desirable personal qualities needed are varied; while it is not too difficult to enumerate these, to attempt an equation in precise terms is only to prove that one's instinct is surer than one's reasoning. (e) Trustees need experience and education, too, in hospital administration. The best hospital administrator is under a great handicap when trustees lack this knowledge.

*Penicillin Administration via the Vagina.* ROBERT I. WALTER, MORRIS A. GOLDBERGER, AND LOUIS LAPID. New York State J. Med., 48: 10, May, 1948.

The authors report 5 patients with gonococcal and/or streptococcal pelvic infections treated intravaginally with calcium penicillin suppositories. The therapeutic results paralleled those obtained with penicillin administered intramuscularly. It appeared that penicillin administered intravaginally is less efficient in terms of amount required than the intermittent muscular route and equally as efficient as the oral route. The use of the vagina as a depot or reservoir of penicillin in the treatment of systemic disease has obvious advantages in the ease of administration, the ability to treat ambulatory patients and in the home, and in not requiring the ministrations of physician or nurse.

*Evidence for an Adrenergic Component in the Nervous Mechanism of Sweating in Man.* H. HAIMOVICI. Proc. Soc. Exper. Biol. & Med., 68: 40, May, 1948.

Administration of Dibenamine (N/N-dibenzyl- $\beta$ -chloroethylamine hydrochloride), a new adrenergic-blocking agent, was found to induce, among other vasomotor effects, inhibition of spontaneous palmar sweating in man. The interpretation of this observation appeared to be at variance with the known concept of the strictly cholinergic innervation of these glands. In this paper, data are presented to show that, in addition to the known cholinergic fibers supplying the sweat glands, there is also an adrenergic component in the nervous mechanism of sweating in man.

*Continuous Fever of Intestinal Origin.* B. B. CROHN AND H. YARNIS. Ann. Int. Med., 26: 6, June, 1947.

A Case Report.



*The Electrocardiogram in Infectious Mononucleosis.* H. L. JAFFE, L. E. FIELD, AND A. M. MASTER. New York State J. Med., 48: 1382, June, 1948.

Pronounced deviations in the T-wave were present in nine of 22 cases (41 per cent) of infectious mononucleosis. In addition to the T-wave changes, the P-R interval was prolonged in two of the cases. These changes were probably the result of organic changes in the myocardium although clinical signs of acute myocarditis rarely occur in infectious mononucleosis. Whenever possible, an electrocardiogram should be recorded routinely in this disease. When abnormalities are present, the period of convalescence should be extended until the tracings become normal. The electrocardiographic alterations in infectious mononucleosis are nonspecific and similar to those that occur in numerous other acute infectious diseases.

## NOTE

### PRESENT HEALTH CONDITIONS IN ISRAEL

The appearance of Volume 1, 1950 of THE HEBREW MEDICAL JOURNAL (Harofé Haivri), inaugurates the 23rd year of its publication under the editorship of Moses Einhorn, M.D.

Written in Hebrew, with English summaries, the Journal is a contribution to improving the health of the new State of Israel, aiding as it does the development of Hebrew medical literature, and thus the newly established Hebrew University-Hadassah Medical School.

In the current number, a symposium is presented on various phases of disease and health in Israel. Among the articles of interest are "Orthopedic Problems in Israel" by I. Pulvermacher, M.D., "Fighting Deafness in Israel" by Ahron Schwarzbart, M.D., and "Kupat Holim—The Labor Health Service in Israel" by Moshé Rabinowitz, director of Kupat Holim in Tel Aviv.

In the section on Bible and Medicine, Dr. C. Genazzani presents a unique essay on "Pathological Symptoms caused by the Famine during the Siege of Jerusalem by Nebuchadnezzar, King of Babylon." In the section on Old Hebrew Medical Manuscripts, Dr. Zussmann Muntner of Jerusalem presents a historical article on "Ascites—A 10th Century Manuscript" by Yizchak Ben Shlomo Ha-Yisraeli. In addition, under the heading of Personalia, are presented biographical sketches on the life and works of Professor Hermann Strauss and Dr. Howard Lilienthal, noted American surgeon.

For more information write to THE HEBREW MEDICAL JOURNAL, 983 Park Avenue, New York 28, N. Y.

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CONTENTS

	PAGE
THE POOL OF MISCIBLE URIC ACID IN NORMAL AND GOUTY MAN, STUDIED WITH THE AID OF ISOTOPIC NITROGEN. <i>DeWitt Stetten, Jr., M.D.</i> .....	149
SODIUM, WATER AND EDEMA. <i>John P. Peiers, M.D.</i> .....	159
THROMBOPHLEBITIS SECONDARY TO ACUTE RESPIRATORY INFECTION. <i>Robert S. Wallerstein, M.D.</i> .....	176
GALLSTONE OBSTRUCTION OF THE DUODENUM: CASE REPORT. <i>Richard M. Alexander, M.A., M.D.</i> .....	183
CASE OF COEXISTENT BENIGN AND MALIGNANT BONE TUMORS. <i>Jacob F. Katz, M.D., and Frederick M. Marek, M.D.</i> .....	187
THE MOUTH IN DIABETES MELLITUS. <i>Emanuel Knishkowsky, D.D.S., Philip Person, D.D.S., and Herbert Pollack, M.D.</i> .....	192
ABSTRACTS .....	203

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THE POOL OF MISCIBLE URIC ACID IN NORMAL AND GOUTY MAN,  
STUDIED WITH THE AID OF ISOTOPIC NITROGEN\*

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*Chief, Division of Nutrition and Physiology, The Public Health Research Institute of The City of New York, Inc.*

Of the many uses to which isotopes may be put in tracer studies, one of the most interesting is the measurement, in the intact animal, of the magnitude of the reservoir of a particular body constituent. This can, in general, be accomplished if one has at hand a supply of the isotopically labeled analog of the compound under investigation which, on administration to the animal, mixes thoroughly with the contents of the reservoir. Additional information may often be obtained from such an experiment in terms of the rate at which new, non-isotopic molecules are arising in the body and entering the reservoir. If, during such an experiment, the size of the reservoir remains sensibly constant, the rate question is termed the "turnover rate" of the compound. Furthermore, some interest often attaches to variations in the magnitude of the reservoir or in the rate of its turnover as produced by some alteration such as disease.

The compound under consideration in the present study was uric acid, the experimental animal selected, for obvious reasons, was the human adult male, and the disease was gout. Whereas, I shall discuss a particular case, the approach employed and the mathematical treatment is quite general and has been applied to such varied problems as the measurement of the total content of body water (1) on the one hand, and the study of the effect of diabetes upon the rate of fatty acid synthesis (2) on the other. The first problem to be considered was the synthesis of isotopically labeled uric acid, and in view of the statutory prohibition against the administration of  $C^{14}$  to human subjects, we elected to use the stable isotope of nitrogen,  $N^{15}$ . In collaboration with Mrs. Jean Benedict and Dr. Peter Forsham (3), isotopic uric acid has been synthesized by two different methods as shown in the first two figures. The first of these was entirely classical, commencing with urea which had been formed by the copper-catalyzed ammonolysis of diphenyl carbonate, isotopic ammonia being employed. Condensation of this material with malonic ester, followed by nitration and reduction, yielded uramil which was then converted to uric acid by condensation with potassium cyanate. In the second procedure, due to Cavalieri, Blair and Brown (4), a few steps were eliminated by employing acetamidomalonic ester in place of malonic ester. Both methods gave identical products labeled, in each case, in the 1 and 3 positions. By starting with the greatest enrichment of  $N^{15}$  available to us, we were able to prepare uric acid containing some 30 atom per cent  $N^{15}$  excess.

When an isotopic variant of a naturally occurring compound is administered to a living organism, it suffers a prompt initial dilution insofar as it mixes, in the

\*A lecture in the series on Recent Advances In Disorders of Metabolism given at the Blumenthal Auditorium, The Mount Sinai Hospital, New York, January 18, 1950.



body, with nonisotopic molecules of the same compound. Clearly, if one knows the isotopic abundance in the compound administered, the quantity of material administered, and the isotope concentration in a sample of the compound isolated immediately after mixing, one can calculate the quantity of nonisotopic

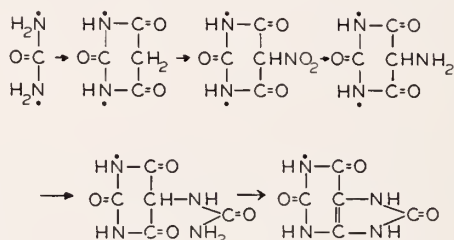


FIG. 1. Synthesis of isotopic uric acid

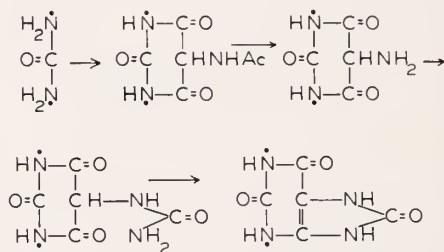


FIG. 2. Synthesis of isotopic uric acid

$$\frac{dA/dT}{O} \rightarrow \boxed{\begin{array}{c} A \text{ gm.} \\ I \% \end{array}} \xrightarrow[I]{-dA/dT}$$

$$K = \frac{dA/dT}{A} = \frac{\ln I - \ln I_0}{T}$$

$$(m = \frac{y-b}{x})$$

$$A = \alpha (I_i/I_0 - 1)$$

$$dA/dT = KA$$

FIG. 3. The arithmetical relationships between the size of the miscible pool, its turnover rate, and its isotope concentration.

diluent, in the present case, the uric acid which mixed promptly with injected uric acid, a quantity that we have called the "miscible pool". In addition to this prompt initial dilution of isotope, there is a second, slow dilution which occurs incident to turnover which, in the present case, results from the body's con-

tinual generation of new, nonisotopic uric acid and simultaneous elimination from the fluids of the body of uric acid which will be a mixture of isotopic and nonisotopic molecules.

If one makes certain simplifying assumptions, which appear to be valid in the light of experimental results, the mathematics of the situation is not complicated (fig. 3). If there are  $A$  gm. of uric acid in the miscible pool which, at time  $T$  has an average isotope concentration of  $I$ , if uric acid is entering this pool at rate  $dA/dT$  unenriched, and is leaving at the same rate but containing  $I$  atom per cent  $N^{15}$ , then it may readily be shown that  $K$ , the fraction of all the uric acid in the pool replaced per unit time is given by the expression on the second line, which is of the form of the equation for a straight line, in which  $-K$  is the slope and  $\ln I_0$  the intercept, when  $\ln I$  is plotted against  $T$ . In the experiments to be discussed we have therefore plotted our data accordingly, drawn the best possible straight lines through the experimental points, and recorded the slopes and intercepts. The antilogarithm of the intercept, in each case, was  $I_0$ , the isotope concentration at zero time, the moment of mixing. Once this is known, the magnitude of the miscible pool, in mg., can be computed from the next to the last expression, where  $a$  is the weight of material administered and  $I_i$  its isotope concentration.  $dA/dT$ , the mg. of uric acid in this pool replaced each day by new, nonisotopic uric acid, may now be calculated simply by multiplying  $K$  by  $A$ . It is worth noting that none of these calculations depend upon notoriously unreliable uric acid analyses which, as is well known, are prone to give false high values.

As to the details of the experimental conditions, normal as well as gouty human male subjects were kept on an adequate though purine-poor diet throughout the experiment. After an initial period of several days, during which the urinary excretion of uric acid came to a steady value, about 50 to 300 mg. of isotopic uric acid were injected intravenously over a half hour interval, and from this point on, urine was collected in 12-hour portions. Each sample was analyzed for uric acid by Archibald's modification of the method of Kern and Stransky (5) as employed by Forsham et al. (6) and from each sample analytically pure uric acid was isolated and analyzed for  $N^{15}$  on the mass spectrometer.

The results of the isotope analyses in the first five experiments are summarized in figures 4-8. Subjects D. C. and R. B. were normal men. It will be seen that, when plotted in accord with our equation, the experimental points do indeed fall close to straight lines, a finding which we have taken to support the validity of the assumptions which we have made. Subject G. W. was also a normal male. In the latter portion of his experiment, he was given four injections of adrenal corticotropin in the hope of gaining some insight into the mechanism of the increase in uric acid excretion which usually follows this treatment. In the present instance, no such increase occurred, perhaps because the preparation was not fully active, and we have therefore provisionally included this subject with the other normal controls. Subject B. S. was a mildly gouty individual with a history of two previous acute attacks, but without clinical evidence of disease at the time of the experiment. Subject A. L., on the other hand, was something of a museum

piece, with a prolonged history of gout, numerous massive tophi, some of which had, in the past, achieved such size as to require surgical excision.

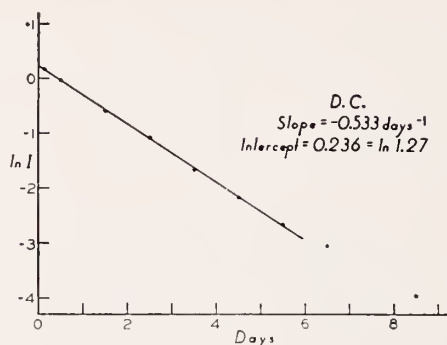


FIG. 4

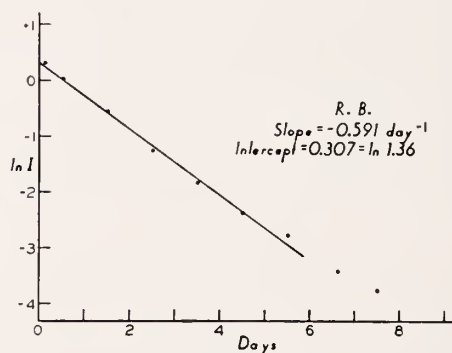


FIG. 5

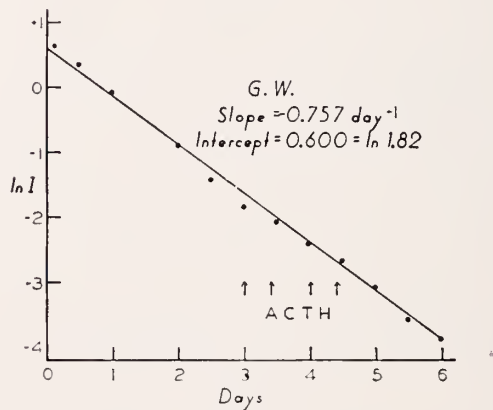


FIG. 6

FIG. 4, 5 AND 6. Isotope concentration in urinary uric acid of normal subject.

The pertinent facts learned from these graphs are tabulated in table I. By the method of least squares we have obtained in each case the most probable value of

the slope and the intercept. Here are recorded in succession the dose injected, its isotope concentration, and the antilogarithm of the intercept which, it will be recalled, was shown to be equal to the isotope concentration of the uric acid in

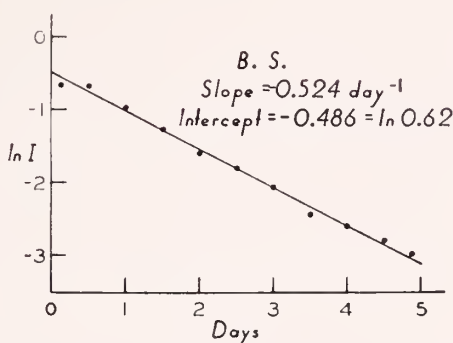


FIG. 7. Isotope concentration in urinary uric acid of mildly gouty subject.

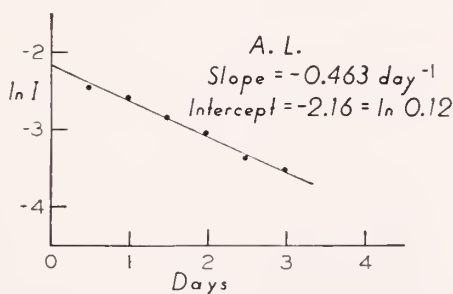


FIG. 8. Isotope concentration in urinary uric acid of severely gouty subject A. L.

TABLE I

*The Magnitude of the Miscible Pool of Uric Acid and Its Turnover in Normal and Gouty Subjects*

SUBJECT	a = DOSE IN- JECTED	I <sub>1</sub> IN- JECTED	I <sub>0</sub> = ANTILN OF IN- TERCEPT	A = MISCIBLE POOL	K = -SLOPE	KA = TURN- OVER	B = URINARY EXCRE- TION	KA - B = SUR- PLUS	C = BODY WEIGHT	A/7C = MEAN CONC. IN BODY WATER	MEAN SERUM LEVEL
	mg.	at. %	at. %	mg.	day <sup>-1</sup>	mg./ day	mg./day	mg./ day	kg.	mg. %	mg. %
D. C.	59.9	29.7	1.27	1341	0.533	715	602	113	73	2.6	6.0
R. B.	56.3	29.7	1.36	1173	0.591	693	563	130	62	2.7	6.2
G. W.	75.0	29.6	1.82	1145	0.757	867	616	251	76	2.2	4.4
B. S.	111.0	29.7	0.62	4742	0.524	2485	468	2017	74	9.2	6.9
A. L.	75.0	29.6	0.12	18450	0.463	8530	416	8114	75	35.1	9.6

the miscible pool at the moment of mixing. From these values, by the equations previously discussed, the size of the miscible pool has been calculated. Considering for the moment only the three normal subjects, you will note that this figure lies in the range of 1150-1350 mg. The fraction of this pool which was replaced by

new uric acid each day ranged from 53 to 76 per cent, amounting to a turnover of roughly 700-850 mg. of uric acid daily.

It is of interest to compare this latter figure with the average daily urinary uric acid excretion during the experimental period, bearing in mind that these values, insofar as they are in error, err on the high side. Despite this fact, in each case the quantity of new uric acid entering the pool exceeds the quantity of uric acid appearing in the urine, the surplus amounting to 100-250 mg. daily. This we take to indicate that the normal body can and does dispose of uric acid by means other than urinary excretion. We are not at present equipped to discuss in detail the fate of this surplus, other than to suggest that significant though low concentrations of  $N^{15}$  were found in some samples of urinary ammonia and urea, indicating that a portion of the injected uric acid did undergo catabolic breakdown. Uric acid in feces, sweat, etc., were not determined.

It is of interest to consider the concentration of uric acid that would be achieved if all of the uric acid in the miscible pool were uniformly distributed throughout all of the water of the body. Taking the body water as maximally equal to 70 per cent of the body weight, we have calculated this quantity, and the results, given in the next to last column, range from 2.2 to 2.7 mg. per cent. It will be noted that the value in each case is approximately half as large as the analytically determined concentration of uric acid in the sera of the corresponding subjects. This finding suggests either that a portion of the uric acid in the body is, by virtue of its location or chemical condition, excluded from the miscible pool or, what appears more likely to us, that uric acid is not uniformly distributed throughout all body fluids and that it is lower in some fluids than it is in serum.

The contrast between the normal and the gouty subjects is striking. Subject B. S., whose disease was not severe, and whose serum uric acid level was not far above normal had, in his miscible pool, about four times as much uric acid as did the normal subjects. Subject A. L., whose serum uric acid was about twice normal, had a pool of miscible uric acid which was about fifteen times normal in size, amounting to something over 18,000 mg. The calculated mean concentration of uric acid throughout the entire body water was, in both gouty patients, higher than the concentration obtained when the corresponding serum was analyzed. In fact, in the severely gouty subject, A. L., this quantity came to about 35 mg. per cent. This value we regard as altogether improbable, as it is far in excess of the expected solubility of uric acid. We are therefore forced to the conclusion that a portion of this 18 gm. of rapidly miscible uric acid was not uric acid in solution but rather was urate in the solid phase precipitated in the cartilages of this patient yet exchangeable with dissolved uric acid.

The deposition of urates in various portions of the body, which is typical of chronic gout, had been proceeding in this patient for a matter of twenty-five years, and on inspection and palpation the guess was hazarded that vastly more than 18 gm. of tophaceous material had been laid down in his joints. Our results suggest that at least the superficial layers of these depositions of solid phase urate were included in the rapidly miscible pool of uric acid, a finding not without interest in its therapeutic implications. Insofar as some of the urate in the solid



phase is capable of rapid equilibration with plasma uric acid, solution of precipitated urate must be taking place, and given the proper conditions it should be possible to effect some degree of resolution of tophaceous deposits.

Interpretation of the turnover values obtained from gouty patients is complicated by these same deposits of urate crystals. What we are measuring in our experimental procedure is the rate at which labeled uric acid in the miscible pool is being replaced by unlabeled uric acid. In the normal subject, in whom there is no reason to postulate the existence of stores of urate in the solid phase, this unlabeled uric acid is believed to have arisen from other purines of the body by well-recognized steps and is therefore a measure of uric acid synthesis. In the gouty subject, whose reserves of solid phase urate may be enormous, another source of unlabeled uric acid exists, namely the slow equilibration of isotopic uric acid in the body fluids with nonisotopic uric acid situated deep in the tophi.

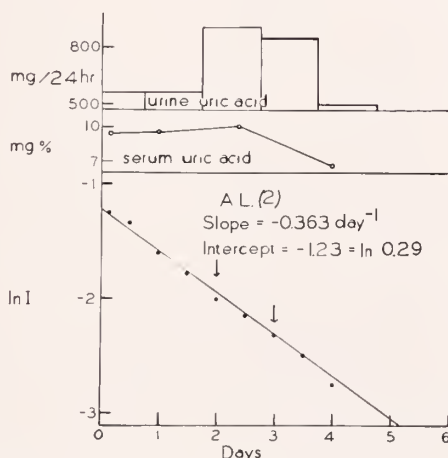


FIG. 9. Second experiment on subject A. L. ACTH was injected at points indicated by the arrows.

Since our experiment does not discriminate between various possible sources of unlabeled uric acid, we are unable to state, at this time, how much uric acid each of these two processes is contributing in the gouty patient.

Since the publication of the foregoing results, my colleagues and I have pursued the study of the metabolic defect in gout. In order to check on our earlier observations, we have repeated a study of our severely gouty patient A. L., after a period of some six months during which medication was intermittent and during the last month of which, no medication was given (fig. 9). After a sufficient number of points had been secured to assure a satisfactory result, this patient was given ACTH at the points indicated by the arrows and this was followed promptly by a satisfactory uric acid diuresis. The finding of coincident decline in the serum uric acid level together with complete lack of change in slope of the isotope data makes it appear that the increase in uric acid excretion, in this situation, resulted not from excessively rapid uric acid formation but rather from an increased renal

clearance of uric acid. This finding, if confirmed, would place the locus of action of ACTH upon uric acid metabolism at the renal level.

The patient was next placed on fairly generous daily doses of salicylates for three months, after which he was rehospitalized and the test repeated (fig. 10). On this occasion, the possible effect of colchicine on the quantities under investigation was sought. Colchicine was administered at the points indicated by arrows, but no alteration in serum uric acid, urinary excretion or slope of isotope decline

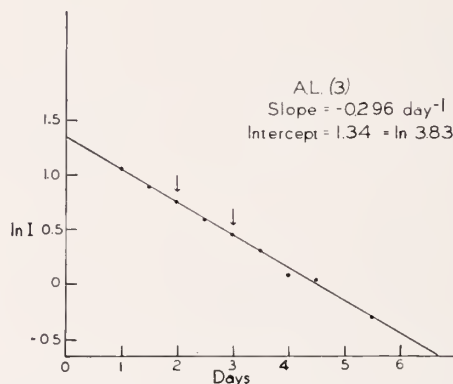


FIG. 10. Third experiment on subject A. L. Colchicine was injected at points indicated by the arrows.

TABLE II  
*Variations in the Miscible Pool of Uric Acid in Gouty Patient A. L. Incident to Therapy or Lack Thereof*

EXPERIMENT	a = DOSE IN- JECTED	I <sub>1</sub> IN- JECTED	I <sub>0</sub> = ANTILN OF INTER- CEPT	A = MISCIBLE POOL	K = - SLOPE	KA = TURN- OVER	C = BODY WEIGHT	A/7C = MEAN CONC. IN BODY WATER	MEAN SERUM LEVEL
	mg.	at. %	at. %	mg.	day <sup>-1</sup>	mg./day	kg.	mg. %	mg. %
1	75.0	29.6	0.12	18450	0.463	8542	75	35.1	9.6 ± .1
2	306	29.6	0.29	31019	0.363	11260	75	59.1	9.5 ± .1
3	300	30.4	3.82	2084	0.296	617	75	4.0	10.2 ± .1

\* Due to injection of ACTH, urinary uric acid values were inconstant.

was noted indicating the absence of effect upon either uric acid production or uric acid excretion.

The calculations from these latter experiments were not without interest (table II). During the interval without therapy, approximately 6 months, the patient's pool of miscible uric acid increased from a value of 18,000 mg. to approximately 31,000 mg. or about 25 times the normal value. This change was not accompanied by any great shift in the level of serum uric acid or other clinical manifestations of the disease. During the succeeding three months, the patient was given 2.4 gm. sodium salicylate daily, and whereas exact information is lacking, spot checks revealed a daily uric acid excretion of approximately 300

mg. in excess of his basal excretory level. At all odds, at the time of the third assay, the pool of miscible uric acid was found to have contracted to a matter of 2,000 mg., about  $\frac{1}{5}$  of the earlier value. Again there was no great change in the serum uric acid level.

These wide fluctuations in the size of the pool incident to medication or lack thereof, make it imperative to consider the boundaries and the compartments of the pool that is being measured. Considering the information obtained from the normal subjects, in whom we assume that all uric acid in the pool is in solution, we learn (table III) that there is about 5.2 times as much uric acid dissolved in non-plasma water as is present in the plasma. The quantity of uric acid in the

TABLE III

*The Distribution of Miscible Uric Acid in the Fluid Compartments of Normal Man*

SUBJECT	A IN TOTAL POOL	B* IN PLASMA WATER	A - B = C IN NON-PLASMA WATER	RATIO C/B
	mg.	mg.	mg.	
D. C. ....	1341	224	1117	5.0
R. B. ....	1173	196	977	5.0
G. W. ....	1145	171	974	5.7
Mean. ....	1220	197	1023	5.2

\* Taking plasma equal to 5.1% of body weight.

TABLE IV

*The Distribution of Rapidly Miscible Uric Acid in Gouty Patients*

SUBJECT	A IN TOTAL POOL	B IN PLASMA WATER	C = 5.2 B IN NON-PLASMA WATER	A - (B + C) IN SOLID PHASE
	mg.	mg.	mg.	mg.
B. S. ....	4742	261	1355	3126
A. L. (1) ....	18450	352	1830	16270
A. L. (2) ....	31019	371	1929	28719
A. L. (3) ....	2084	382	2008	(-306)

plasma compartment is calculated from the serum uric acid concentration and the estimated volume of plasma (body weight  $\times$  0.051). A further provisional assumption is now made that this distribution between uric acid in solution in plasma water and uric acid in solution in remaining body water is determined by the volumes of water in the two compartments and Donnan effects which are unaltered in gout. Operating on this assumption, we can now review our data from gouty patients and assign quantities to the uric acid in each of three compartments (table IV). The uric acid in the plasma is here calculated, as above, from the serum uric acid concentration, that in solution in non-plasma water by multiplying the plasma uric acid by the factor 5.2. The remainder of the uric acid in the miscible pool, the difference between the uric acid in the total pool and that presumed to be in solution in one or another compartment, we provi-

sionally term "miscible solid phase urate". It must be admitted that we have no direct experimental evidence at the moment for the assignment of this surplus uric acid to the solid phase but it is difficult to picture any other site capable of containing such large and variable amounts of material. This question is currently under investigation. From table IV, it will be seen that it is the quantity in this compartment that is subject to wide excursions. When no medication was allowed, it increased enormously, while under protracted salicylate therapy, it apparently completely disappeared, since at the end of the period of medication the total miscible pool had contracted to a value such that its contents could entirely be accounted for by uric acid in solution.

It is worth noting that even though salicylate therapy resulted in a decrease in size of the miscible pool of uric acid to values but little above normal, the patient still has massive palpable and visible tophi which are clinically undiminished. This fact confirms our view that whereas a portion of the urate in the solid phase may, in the gouty individual, be included in the rapidly miscible pool, certainly a portion of the tophaceous urate is excluded from this pool. It is easy to suppose that the more recently precipitated urate at the periphery of the tophus, which is still in contact with body water, is included in the miscible pool and is still resolvable under the influence of such agents as salicylate, while the dry, chalky urate deposits of older vintage are excluded from the pool of miscible uric acid and will not be redissolved under similar circumstances. The previously unpublished results included herein, will be described in a more detailed report elsewhere in the very near future.

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## SODIUM, WATER AND EDEMA

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It has been established beyond reasonable doubt that the osmotic pressure throughout all the media within the mammalian organism is uniform. This signifies that the boundaries between these media permit the free passage of water by the mere process of diffusion. It also means that the distribution of water between two contiguous media separated by such a boundary or membrane will be determined by the relative concentrations in the two media of osmotically active components which are unable to cross the membrane freely by diffusion. In the exchanges of fluid between blood capillaries or lymph capillaries and the perivascular spaces the effective osmotic force is exerted by the proteins alone. Although the osmotic pressure of the proteins is only a small fraction of the total osmotic pressure of the blood plasma, the other osmotically active constituents play no part in these exchanges because, since they diffuse freely across the vascular and lymphatic membranes, they contribute equally to the osmotic pressure in both media. A system of this kind in which a restrained substance occurs predominantly in one of the two media is not in true equilibrium. This can be achieved only by the interposition of some physical force which will counteract the unbalanced osmotic pressure. In the blood capillaries this force is the capillary blood pressure.

In exchanges of water between the cells and the extracellular fluid, no such physical force is required. The cells can be regarded as perfectly elastic. Distribution of water is determined by the balanced osmotic pressures in the two media produced by the osmotically active components to which the cell membranes are impermeable. This impermeability is the property upon which the differentiation of cellular media depends. In this system again, distribution and exchanges of water are determined, not by the total osmotic pressure, but by the partial osmotic pressures in each medium of those components which are restrained by the interposed membrane. This will be termed the *effective osmotic pressure*. In a system through which water diffuses freely, both total and effective osmotic pressures must be uniform, but total osmotic pressure may be altered without any disturbance of the distribution of water so long as the osmotic change involves only an unrestrained component. The classical example of such a component is urea, which appears to traverse all membranes with perfect freedom. If the concentration of urea in the body is greatly elevated by ingestion or injection of the compound, no shift of fluid between cells and extracellular fluid can be detected. The volume of distribution of urea in the body is found to be equal to the total volume of water in the body.

In the extracellular fluid, such an overwhelming proportion of the effective



osmotic pressure is contributed by sodium salts that, under any but the most exceptional conditions, sodium serves as a measure of the effective osmotic pressure. It follows that sodium is the major instrument by which the distribution of water within the body, and consequently the state of hydration of the cells, is controlled. If the concentration of sodium in the serum (in this connection the terms serum and extracellular fluid will be used synonymously since their compositions are so closely correlated) rises, the cells of the body will give up water and contract. They will become dehydrated and their contents will become overconcentrated. If the concentration of sodium salts in the serum falls, the cells will take up water and swell. They will become overhydrated and their contents will become overdiluted.

It is, of course, possible for disturbances of effective osmotic pressure to originate in the cells. In fact, it is inconceivable that cellular activity could proceed without varying intracellular osmotic pressure. But such disturbances can be detected and adjusted only through the extracellular fluid. Usually, since they are localized, their effects are buffered or dissipated in this homogeneous environment. Welt, Orloff, Kydd and Oltman (1) have recently shown that under certain conditions intracellular activities may have osmotic effects of catastrophic proportions. In the course of a therapeutic electric shock lasting only 55 seconds, sodium, chloride and potassium of the serum rose approximately 10 per cent above their initial values, indicating that this proportion of the extracellular water had been drawn into the cells. The process was reversed almost as rapidly after the electric current was cut off. Presumably extreme metabolic activity of the largest single mass of cells in the body, the muscles, resulted in a sudden increase of osmotic pressure within the cells. That muscular activity was responsible for the transfer was verified by the fact that the electrolyte changes were inhibited by curare. Welt has suggested in this and other connections that conditions may be discovered in which a primary disturbance of the osmotic pressure of the cells relative to their other properties or components might lead to a readjustment of the mechanisms for the regulation of exchanges of salt and water. More specifically he has proposed that in certain states such as pulmonary salt wastage, in which sodium is not conserved by the kidneys, although these organs appear to be functionally competent, the primary error may reside in a deficiency of the effective osmotic components in the cells, to which the organism responds by maintaining a hyponatremia. This would not change the essential character of the automatic regulating devices. The osmostat would continue to operate, but would respond at a different effective osmotic pressure—that is, at a lower concentration of sodium.

Among the properties of the body which appear to be sedulously guarded by automatic mechanisms are the volume, the distribution and the composition of the body fluids. As far as supply and demand are concerned, the volume and composition of the body fluids depend upon the intake and output of fluid, salts and other materials; the distribution and concentration of the body fluids depend upon the effective osmotic pressure of the extracellular fluid which is ordinarily a function of the concentration of sodium salts. Sodium may, and

undoubtedly does, have other more specific functions than the maintenance and control of the effective osmotic pressure of the extracellular fluid, but they are so masked by this preeminent function that it is next to impossible to recognize them. It follows that the most important problem in the elucidation of water metabolism both in health and disease is to discover the mechanisms by which the ingestion and excretion of water and sodium salts are mutually and automatically regulated.

Ultimately maintenance of the composition and volume of the internal environment depends upon the kidneys, and especially upon the terminal segments in which sodium and chloride are reabsorbed. Of these two components sodium can be completely reabsorbed, but the reabsorption of water, presumably the terminal process in the elaboration of urine, is limited by the quantity of solutes remaining in the tubules. These consist, in addition to sodium salts, of a number of substances which, having been filtered through the glomeruli or secreted by the tubules, partly or completely escape reabsorption. The most important of these ordinarily is urea, a major component of the urine. Urea appears to be reabsorbed by back-diffusion, the proportion returned to the blood being a relatively fixed fraction of the quantity filtered. The quantity left in the urine is, therefore, proportional to the concentration of urea in the blood plasma and the rate of glomerular filtration, which may be quite independent of the supplies of water and salt in the body. Nevertheless, the ability of the kidney tubules to reabsorb water is limited by the quantity of urea remaining in the tubular fluid. Urea and all other solutes that are not reabsorbed, or are reabsorbed to a limited extent, in the process of excretion impose upon water an obligation that is quite independent of the volume and the effective osmotic pressure of the urine. The excretion of these substances and the quantity of water they preempt depend instead upon the metabolic activities of the body. Among other substances of this kind, glucose in the diabetic, sucrose, and other sugars that can not be utilized, mannitol and sulfates deserve mention because they have been used as diuretics or for the investigation of renal function. Whatever sodium chloride may escape reabsorption preempts water in a similar manner; but this salt differs from urea and the other substances mentioned above inasmuch as it can be reabsorbed by an active process to any extent. It can even be withdrawn completely from the urine. The obligation of water to urea and related solutes is, therefore, inescapable, while its obligation to sodium chloride is facultative, depending upon the degree to which this salt is reabsorbed. Furthermore, sodium chloride enjoys a greater measure of freedom than water and holds a position of priority in the regulation of the volume and effective osmotic pressure of the body fluids, which ultimately depend upon the quantities of salt and water reabsorbed by the renal tubules. Urine can be free from salt, but a urine free from water is inconceivable.

Although all the sodium salts and water that ultimately find their way into the urine originate in the glomerular filtrate, the relation of the excretion of sodium to the rate of glomerular filtration appears to be almost fortuitous. To be sure, since more than 99 per cent of filtered salt and water are usually reab-

sorbed in the tubules, not only the concentration, but also the quantity of reabsorbate must be almost identical with those of the filtrate; but a variation of 1 per cent in the proportion of filtrate reabsorbed will alter the rate of excretion of either water or salt far more than a larger variation of the volume of filtrate will if the proportion of filtrate reabsorbed remains the same. If, for example, instead of 99 per cent of a given volume of filtrate and its contained salt, 98 per cent is reabsorbed, the excretion of salt and water will be doubled. But if the volume of filtrate is increased by 10 per cent, while the proportion reabsorbed remains 99 per cent of the total, the change in excretion will amount to only 10 per cent. Unless, then, the proportion of filtrate reabsorbed diminishes as the volume of filtrate increases, which does not generally seem to be the case, excretion of both salt and water must be controlled predominantly by the degree to which they are reabsorbed from the tubules, not by the quantities that find their way through the glomerular filters.

Reabsorption of water, as far as this is not under obligation to solutes that have escaped reabsorption in the tubules, appears to be controlled by the anti-diuretic hormone of the posterior lobe of the pituitary, which promotes the terminal reabsorption of water. When posterior pituitary antidiuretic activity is maximal, therefore, the urine volume will be as small as may be compatible with the load of solutes requiring secretion; that is, the concentration of urine will be maximal. The normal stimulus to posterior pituitary antidiuretic activity appears to be the effective osmotic pressure of the serum. This hypothesis is supported by a mass of inferential evidence and by direct evidence adduced by Verney and his associates (2, 3). They found that discharge of antidiuretic hormone was provoked by injecting hypertonic saline solution into the internal carotid arteries of animals. Hypertonic glucose solution had a similar, but less potent effect. Urea solutions of the same osmotic pressure were altogether ineffective. The primary function of this hormone must be to preserve the effective osmotic pressure of the extracellular fluid.

Presumably reabsorption of sodium chloride is under some similar hormonal control, but this agent and the stimulus to its activity have not been so clearly established. Indirect evidence would place the source of the hormone in the adrenal cortex and suggest that its action is similar to that of the synthetic steroid, desoxycorticosterone acetate. The function of this salt-retaining hormone must be the protection of the volume of fluid in the body, the stimulus to its discharge reduction of this volume or some variation that is usually linked with reduction of the volume of fluid in the body. This is a most elusive function. To identify it precisely is one of the most crucial problems of water metabolism and renal physiology. In spite of the uncertainty about the nature and origin of the salt-retaining hormone, the term *adrenocortical* will be applied to it in this discussion for purposes of convenience, in a symbolic sense, at least. The name is a matter of indifference except insofar as it assumes that reabsorption of sodium is under hormonal control. Actually, the discussion will be concerned with the reabsorption of sodium chloride as a physiological function, irrespective of the agency by which it is controlled.

Although the behavior of the kidneys will be discussed chiefly with reference to the actions of these two hormones, this does not imply that excretion of sodium chloride and water is solely governed by them. It has been clearly demonstrated by Verney and his associates (4) and others (5) that the nervous system exerts an influence quite apart from that of the hormones. It is still an open question whether this influence is exercised entirely through the circulation. There can be no doubt, however, that disturbances of the renal circulation can affect the excretion of salt and water. Changes of acid-base equilibrium, which is inextricably entangled with osmotic equilibrium, may manifest themselves in alterations of the excretion of salt and water. All these associated factors will, however, only modify, in certain instances, the actions of the hormones. It will not, therefore, be altogether presumptuous to inquire how far the phenomena of edema can be explained in terms of the actions of antidiuretic and adrenocortical hormones, and to propose that explanations of edema must be compatible with the demonstrated actions of these hormones and the physico-chemical principles that determine movements and exchanges of fluid within the body.

In the normal subject who is permitted to take and able to absorb fluid according to physiological dictates, the excretions of water and of sodium chloride are directly attuned to the intakes of these commodities and to their concentrations in the serum (if it be permissible to speak of the concentration of water). In the dehydrated or hydropenic subject, this is not the case. In such a subject reabsorption of sodium chloride will be augmented and the concentration of sodium and chloride in the serum will rise. Under these circumstances the excretion of sodium may even appear to be inversely related to its concentration in the serum. This is a direct consequence of the fact that the stimulus to reabsorption of sodium is controlled by the volume of fluid in the body. When this is reduced, reabsorption of sodium chloride increases. This reaction, which has been termed the *dehydration reaction*, has a protective effect. In the state of dehydration there is need to conserve the extracellular fluid. As this diminishes, reabsorption of sodium chloride is accelerated. This removes from the urine a solute that would limit reabsorption of water. Because of accelerated reabsorption of salt, the concentration of sodium in the serum rises. This provokes the discharge of antidiuretic hormone to further curtail the excretion of water. At the same time it draws water from the cells to the extracellular fluid, thereby forcing the cells to assume their share of the burden of dehydration and prevent the extinction of the extracellular fluid. This reaction can be elicited by administration of excessive amounts of salt, by deprivation of water, by administration of dehydrating agents or by any procedure that depletes the body of water in excess of salt. An excessive concentration of sodium in the serum is almost invariably a sign of dehydration. If the animal with such a condition has free access to water and the ability to drink and absorb water, the condition is rectified under the stimulus of thirst. A primary retention of sodium salts, whether it be produced by desoxycorticosterone acetate or any other influence, will not, therefore, manifest itself in any considerable elevation of serum sodium in a free person. For our purposes it is equally important to recognize that the effect of any measure that



affects the excretion of salt and water upon the excretion of sodium will be conditioned by the antecedent state of hydration of the subject.

At this point it becomes necessary to modify the premises of this argument slightly. The actual regulator of antidiuretic activity may not be—perhaps it would be safe to say, is not—the effective osmotic pressure of the extracellular fluid, but the state of hydration of the cells of which the effective osmotic pressure of the serum is our only criterion. By the same token the regulator of the reabsorption of sodium salts is not the total volume of fluid in the body, but the volume of the extracellular fluid (or some function usually related to the volume of the extracellular fluid). In this connection it may be well to recall attention to the fact that the effect of the addition or removal of any fluid from the body upon the volume of the extracellular fluid is the resultant of two factors: the exchange with the external environment and the exchange with the cells. Addition of a hypertonic solution of sodium chloride, for example, expands the volume of the extracellular fluid not only by the increment of fluid administered, but also by an increment withdrawn from the cells. A hypotonic solution, on the other hand, expands the extracellular fluid by less than the volume added because the cells take up part of the increment of water.

The administration of hypertonic salt solution induces diuresis, in spite of the fact that, by increasing the effective osmotic pressure of the serum and drawing water from the cells, it must stimulate antidiuretic activity. Withdrawal of water from the cells, however, expands the volume of the extracellular fluid, thereby inhibiting reabsorption of salt. This salt limits reabsorption of water by the kidney. The best that the antidiuretic hormone can do, therefore, is to restrict the water excretion to the minimum required for the excretion of the sodium chloride that escaped reabsorption. So long as adequate water is supplied, salt and water are excreted freely. If, however, the supply of water is limited, the volume of extracellular fluid ultimately becomes contracted. At this point the dehydration reaction is brought into play: reabsorption of salt is accelerated and excretion of water diminishes. Excretion of salt in the first instance appears not to be a simple function of the concentration of sodium in the serum, but a reaction to the expansion of extracellular fluid.

Much attention has been given to a process termed *osmotic diuresis*. It has been claimed that the ultimate quantity of water reabsorbed from the renal tubules is limited by the total load of solutes requiring excretion. This implies that the reabsorption of water is limited by the osmotic pressure of the urine, regardless of the nature of the components that make up the osmotic pressure. It is also claimed that, if the load of non-reabsorbable solutes delivered to the tubules by the glomeruli is too great, reabsorption of sodium chloride is inhibited. Among osmotic diuretics have been grouped sodium chloride and other salts, urea, sugars, mannitol and other compounds that are filtered, but not reabsorbed. It is implied that all have a similar reaction, not only producing diuresis, but also increasing the excretion of salt (6, 7, 8). This would locate the control of the excretion of water and salt in the kidney itself, divorcing it largely from the influence of the hormones. It would also contravene the automatic regulatory



system that has been proposed by putting the reabsorption of salt at the mercy of other solutes. It has already been pointed out that the effect of any measure on the excretion of sodium is conditioned by the state of hydration of the subject. In a well hydrated subject hypertonic sodium chloride solution is excreted with great celerity in high concentration; but, as the supply of water in the body becomes depleted, reabsorption of salt progressively increases and the concentration of sodium chloride in the serum rises. Kerpel-Fronius (9) and McCance and associates (10, 11) found that urea, when given to a hydropenic subject, reduces the excretion of salt. Mudge, Foulks and Gilman (8) and others have given urea with sodium chloride. Under these circumstances the combined osmolar concentrations of urea and sodium chloride in the urine have tended to remain relatively constant, not because reabsorption of water was limited by the osmotic pressure of the urine, but because excretion of sodium chloride diminished as the load of urea was increased. That is, the reabsorption of sodium chloride increased and its concentration in the serum rose in proportion to the need for conservation of water as a result of the diuretic effect of urea. Seldin and Tarail (12) found that the diuresis induced by intravenous injections of 10 per cent urea solution had no effect upon the excretion of sodium chloride by well hydrated subjects, but retarded the excretion of salt by hydropenic subjects. In the latter, in other words, urea provoked the dehydration reaction. This corroborated Kerpel-Fronius' (9) earlier observation. Large injections of 25 per cent solutions of glucose or mannitol, on the other hand, not only induced profuse diuresis, but also increased the excretion of sodium chloride. The elimination of salt increased less and for a shorter time in hydropenic subjects than it did in well hydrated subjects. Since the osmotic effects of glucose and urea in the renal tubules were the same, the cause for their different effects must be sought elsewhere. The most obvious difference between glucose and mannose on the one hand and urea on the other lies in their diffusibility. Because it penetrates cells freely, urea does not alter effective osmotic pressure, while glucose and mannitol, which are restrained by cellular membranes, do. Verney and O'Connor (2, 3) discovered a similar difference in their studies of antidiuretic activity. Hypertonic salt solution and hypertonic glucose solution evoked antidiuretic activity, but urea solutions with equally high total osmotic pressure did not. In the glucose experiments of Seldin and Tarail (12), at the height of the diuresis, when sodium and chloride are being excreted rapidly, the concentrations of these ions in the serum are greatly depressed, not because they have been sacrificed in the urine, but because the increment of osmotic pressure contributed by the glucose has drawn water from the cells. As the concentration of glucose in the serum falls, the excretion of salt diminishes and the concentrations of sodium and chloride in the serum rise to their original levels. Mannitol behaves in a similar manner, but its action is more vigorous and prolonged than that of glucose because it can not be oxidized. In both cases, inhibition of the reabsorption of sodium chloride appears to be a reaction, not to the osmotic effect of the diuretic in the urine (in this respect glucose and mannitol do not differ from urea), but to the effects of glucose and mannitol upon the effective osmotic

pressure of the serum and the hydration of the cells. Glucose and mannitol behave in the latter respect like so much sodium chloride. The body in response employs its usual instrument, sodium chloride, to rectify the disturbance of the effective osmotic pressure. In this as in other reactions less salt was sacrificed by dehydrated subjects. The excretion of salt, like the discharge of antidiuretic activity, appears to be attuned not to the concentration of sodium in the serum, but to the effective osmotic pressure. Or more precisely, the excretion of water is controlled by the contraction of the intracellular fluid, the excretion of salt by the expansion of the extracellular fluid, induced by the rise of the effective osmotic pressure of the latter.

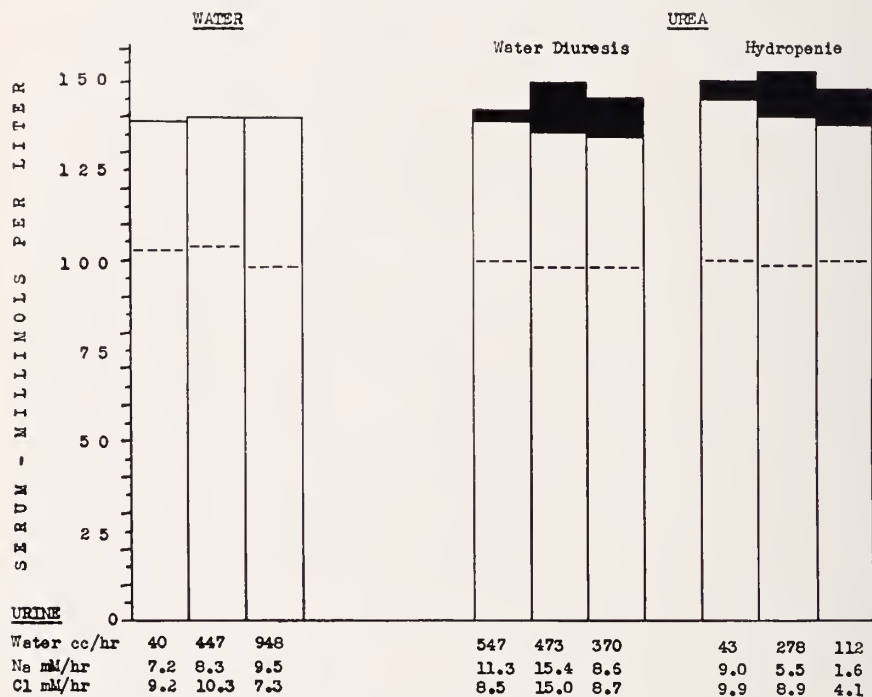


FIG. 1

These phenomena can be summarized by a few illustrations constructed from data of Seldin and Tarail (12). In Figure 1 the total heights of the open columns represent the concentrations of sodium in the serum, the broken lines the concentrations of chloride, both in milliequivalents per liter. The latter are inserted merely to show that changes of sodium and chloride parallel one another. The first column in each pile represents the initial or pretreatment state; subsequent columns the state at intervals during the experiment. Below the columns are given the rates of excretion of water, sodium and chloride at the times of the analyses of serum. The first pile of 3 columns illustrates the effects of the ingestion of 1250 cc. of water per hour. In spite of the large diuresis, the excretion of sodium and chloride is not appreciably altered.

The second and third piles illustrate the effects of the rapid intravenous injection of 500 cc. of 10 per cent urea in 5 per cent glucose solution (the glucose had to be added because solutions of urea alone lake red blood cells). The first experiment was made when the subject was receiving water, the second when the subject had been deprived of water. The black extensions of the columns represent the osmolar concentrations of urea in the plasma. The total height of the columns, therefore, represents the osmolar concentration of sodium salts plus urea. This rises slightly in both experiments, while the concentration of sodium diminishes slightly. These changes are presumably referable to dilution by the injected fluid and failure to obtain complete equilibrium. Calculations from the

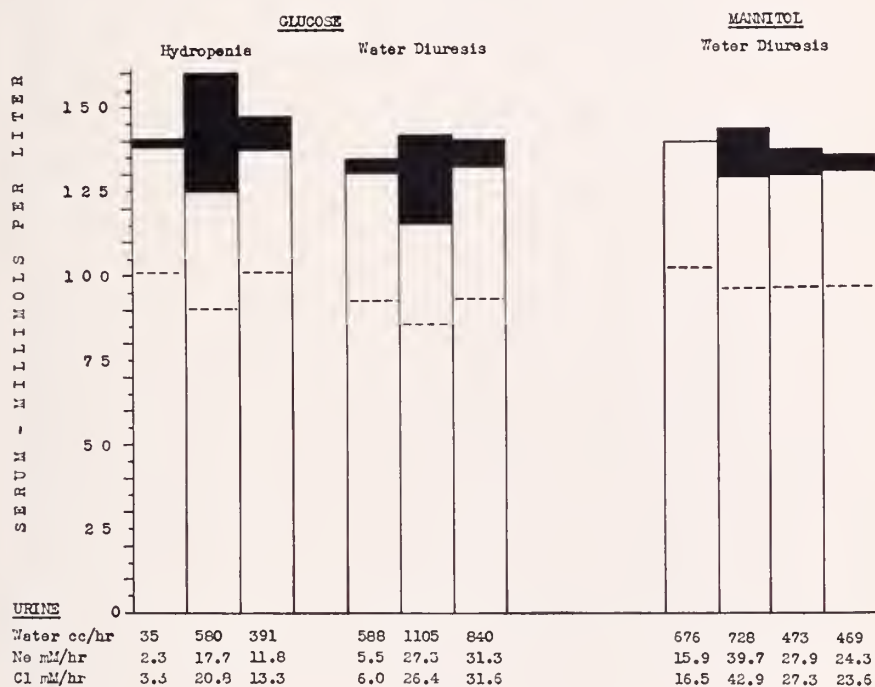


FIG. 2

chloride space revealed no appreciable exchange of fluid or electrolytes between cells and extracellular fluid. Although there was a profuse diuresis in the first experiment, the excretion of sodium and chloride did not change significantly. In the hydropenic state the diuresis was distinct, but of smaller magnitude; the urinary excretion of sodium and chloride diminished.

Figure 2 shows the effect of the intravenous injection of glucose and mannitol. The black extensions to the columns represent osmolar concentrations of glucose or mannitol. In the first experiment 1000 cc. of 25 per cent glucose solution was rapidly injected into the vein of a subject who had been previously deprived of water. Shortly after the injection serum sugar had increased strikingly, its concentration being equivalent to 30 milliosmols of sodium chloride, 1080

milligrams per cent. Simultaneously the concentration of sodium fell sharply 13.5 milliequivalents. These changes are more than twice as great as those produced by an equivalent amount of urea shown in the preceding slide. By estimation from the chloride space the extracellular fluid in the interval appeared to have expanded to the extent of 1.8 liters at the expense of cellular water. The excretion of sodium and chloride rose sharply and remained elevated, but not quite so much elevated, in the last period when the concentration of glucose in the serum had begun to fall and the diuresis was abating. The second set of columns illustrates the effect of 600 cc. of 25 per cent glucose solution injected intravenously into a subject who received simultaneously water by mouth. The rate of water excretion is far greater and the excretion of sodium chloride is comparably increased and prolonged, although the dose of glucose was smaller than that given in the first experiment. In the last set of columns the effect of the injection of 400 cc. of 25 per cent mannitol is shown for comparison. In general, mannitol behaves like glucose, depressing the concentrations of sodium and chloride in the blood serum and increasing their excretion in the urine. Although less mannitol than glucose was given, the diuretic effect of the former was more prolonged, probably because mannitol can not be oxidized. The only channel for removal, therefore, is the urine.

In normal subjects, to which attention has been thus far confined, it has been quite possible to correlate reabsorption of sodium chloride with the volume of the extracellular fluid without enquiring into the precise property by which the adrenocortical or salt-retaining receptor is apprised of the need for conservation of salt. The site of this receptor is even more obscure. Examination of edematous states at once excludes as the criterion the total volume of the extracellular fluid. The kidneys are quite indifferent to the presence of thrombophlebitic or lymphatic edema so long as it keeps its place. Indeed it is hard to conceive how these organs would be apprised of such a local accumulation of fluid. It would be unfortunate if they responded with diuresis, because this would lead to dehydration of all the rest of the body in behalf of the affected part. As a matter of fact, while such an edema is accumulating, the reabsorption of water, chloride and sodium increases; when it is discharged, reabsorption diminishes. The actual cause, not only of these edemas, but of all edemas, is the escape of fluid from the blood stream more rapidly than it is returned. During the accumulation of localized congestive edema, hemoconcentration can be detected; the volume of the circulating blood diminishes. During delivery of the edema, when the fluid is returned to the circulation, the blood volume increases. This would lead to the conclusion that it is the volume of the circulating blood which governs the reabsorption of salt. This may be adopted as a first approximation, with the reservation that the actual regulatory agency may be, not the volume of the circulating blood, but some function or functions usually associated with the volume of the circulating blood, just as the stimulus to reabsorption of water is not the concentration of sodium in the serum, but the effective osmotic pressure of the serum, or probably the state of hydration of the cells.

If, by plasmapheresis and low protein diets, the serum albumin of a dog is



depleted, the volume of extracellular fluid increases progressively, culminating in the appearance of demonstrable edema. Weech and associates (13) showed that as serum albumin falls the volume of the circulating plasma diminishes because the decrease of the colloid osmotic pressure of the plasma promotes transudation from the blood capillaries. The concentrations of sodium and chloride in the serum remain unchanged. Salt is retained in proportion to water. A similar sequence is seen in patients with edema from malnutrition or nephrosis. Ingestion of salt will aggravate, while restriction of salt will alleviate, the edema. On the other hand, variation of the intake of water over wide limits will have little or no effect. This seems to be an illustration of the priority of salt. The edema itself, however, is not produced primarily by the failure of the kidney to excrete salt, but by loss of fluid from the circulation. This can be readily demonstrated by the intravenous injection of serum albumin or other colloids that are retained in the circulation. By restoring the colloid osmotic pressure of the serum they draw fluid into the blood stream, whereupon diuresis results. In this diuresis, salt and water are discharged in equivalent amounts. If the individual is then given a diet with restricted salt, edema will reaccumulate only in proportion to the amount of sodium retained (14).

In terms of the preliminary discussion, the sequence of events in the formation of edema could be formulated in the following manner: Loss of fluid from the blood stream in consequence of the reduced serum albumin diminishes the blood volume, the signal that fluid volume is threatened. This evokes an adrenocortical discharge which promotes reabsorption of salt by the kidneys. The resulting increase of sodium in the serum stimulates antidiuretic activity. This process continues until a new equilibrium is reached in which the loss of fluid from the blood stream and its return are equal. Except for the initial event the course would be almost the same if an increase of capillary blood pressure as a result of venous congestion were substituted for a reduction of serum albumin, because both would cause transudation of fluid from the blood stream. One difference may be significant. In the edema due to increased hydrostatic pressure, the colloid osmotic pressure of the blood would be absolutely elevated; in the edema of hypoalbuminemia it would be depressed.

One objection to this simple explanation immediately presents itself. Why should antidiuretic activity persist? Why should not water excretion proceed since the effective osmotic pressure of the serum is not elevated? I should like to suggest that antidiuretic activity does not persist, tentatively, because this would seem to contradict much experimental evidence. Antidiuretic activity during the accumulation of edema has been admitted and can be reasonably explained. The effect of salt in exaggerating edema is equally susceptible to explanation. But, once an equilibrium is reached, water alone is excreted with facility with no evidence of antidiuretic activity. Edema fluid *en masse* is the product of the interplay of capillary blood pressure, as opposed to tissue tension, of colloid osmotic pressure of the blood serum as opposed to that of the pericapillary fluid, and of lymph flow. Its composition may be altered by processes of diffusion so that sodium salts rapidly distribute themselves through the



edema fluid as they do through the remainder of the extracellular fluid; but its volume can be altered only by varying the factors that influence transudation. Edema fluid is effectually exteriorized. So long as salt is not given, or insofar as water is given in excess of salt, it can pass through the system freely; but so soon as any additional water is excreted, the volume from which it can be drawn is limited almost entirely to the fluid in the circulation. Such a withdrawal would immediately raise the effective osmotic pressure of the serum which would provoke antidiuretic activity, automatically checking the discharge of water. Just as soon, however, as the circulating blood volume is expanded by reabsorption of the edema fluid, the restraint on salt excretion is broken and true diuresis ensues.

The priority of salt over water in the production of edema derives from two sources: first, reabsorption of water is controlled by the concentration of sodium in the serum; second, water is obligated in the kidneys to other solutes requiring excretion. In an earlier paper (14) the following explanations were offered for the relative effects of water and salt on edema. An excess of water has a more or less neutral effect because it dilutes the sodium in the body, which merely inhibits antidiuretic activity, permitting the administered water to be excreted. Limitation of water increases the concentration of sodium in the serum, thereby stimulating antidiuretic activity. An excess of sodium increases the concentration of sodium in the serum, exaggerating the dehydration reaction and stimulating antidiuretic activity as well. It is intolerably cruel to give extra salt without water. Limitation of salt tends to diminish the concentration of sodium in the serum, thereby minimizing the dehydration reaction and antidiuretic activity.

To assess the role of blood volume upon the excretion of salt and water and at the same time analyze the diuretic action of serum albumin, Goodyer, Relman and Peterson (15) loaded themselves with water or 0.2 per cent salt solution. This was intended to stabilize the rate of excretion of water and salt. Under these circumstances injections of serum albumin distinctly retarded the excretion of water and salt. The subjects of these experiments were, however, already in a state of polyuria induced by hypotonic solutions. The body fluids were, therefore, presumably slightly overexpanded with water in excess of salt so that antidiuretic activity was already effectually inhibited and the stimulus to excrete extra sodium was also in abeyance. When Welt and Orloff (16) gave smaller amounts of water and injected 25 per cent serum albumin, the excretion of water did not change, but the elimination of salt diminished. When the albumin was given as a 4 per cent solution in normal saline, however, more water and salt were excreted than after an equal quantity of normal saline alone.

In all these experiments, including the last, the albumin expanded the volume of the circulating plasma. In the normal human subject, then, either expansion of the blood volume by means of albumin does not inhibit the reabsorption of sodium or the effect of this expansion is obscured by some other reaction. There is a difference between the injection of albumin alone, which did not produce diuresis, and the injection of diluted albumin which did. In the former not only

was plasma volume expanded, but in addition the colloid osmotic pressure rose. When the diluted albumin was injected the plasma volume expanded, but the colloid osmotic pressure of the plasma did not rise. When serum albumin alone was injected, fluid was drawn into the blood stream from the extracellular space; when diluted albumin was injected, the fluid was introduced with the albumin, which only served to retain the fluid in the blood stream. An increase of the colloid osmotic pressure of the plasma is ordinarily a sign of hemoconcentration. This of itself would constitute an indication for conservation of fluid and salt. These experiments would suggest that hemoconcentration, evidenced by increase of colloid osmotic pressure, promotes reabsorption of sodium salts, while expansion of the volume of the circulating blood inhibits the reabsorption of sodium salt. The action of serum albumin may, then, depend upon its relative effect upon these two functions. It is for this reason that I suggested above that the effects of increased capillary pressure might not be altogether identical with those of diminished colloid osmotic pressure. When serum albumin is low and there is a large body of edema fluid available, the expansion of plasma volume will be maximal; serum albumin can not increase to an inhibitory level. In the normal or dehydrated person the plasma volume will increase proportionally less than the colloid osmotic pressure, which will, therefore, become the determining factor.

In another experiment the sequence of events after injection of albumin into nephrotic patients was examined (17). The primary event was a profuse diuresis without acceleration of the excretion of sodium chloride. This caused the concentration of sodium in the serum to rise, whereupon urinary sodium chloride rapidly rose. Such a sequence of events has been described from time to time in connection with various diuretics. It has been suggested that sodium is not excreted until its concentration is elevated, making more available to the kidneys. This implies a direct relation between the excretion of sodium and the quantity filtered that is not physiologically substantiated. In the outline of the sequence of events in the development of hypoalbuminemic edema it was concluded that the terminal event should be retention of water. It might be argued, therefore, that in the reversal of this process the primary event should be discharge of water. In this case, however, the process was not truly reversed; that is, the course of its development was not precisely retraced. There is another possible explanation for the order of events. When the albumin is introduced, fluid is at once drawn from the extracellular accumulation into the blood stream. Since antidiuretic activity is in abeyance, the water in this fluid becomes immediately available for excretion; inhibition of reabsorption of sodium, on the other hand, will be delayed until the initial sharp increase of colloid osmotic pressure is modified by dilution and the volume of circulating plasma is appreciably expanded.

Ascites, especially the ascites of liver disease, presents a peculiar problem. In no other condition is edema fluid so effectually trapped and the trap so firmly locked. If a patient with cirrhotic ascites also has peripheral edema, the latter can usually be discharged by intravenous albumin, but the ascites defies albu-

min. It has been claimed that hypoalbuminemia is not the determining factor in the production of ascites. In a sense this is true, but it is also true of every other kind of edema. The mere process of accumulation of edema is dictated by the Starling principle which rests on thermodynamic laws. Ascites resembles lymphatic edema inasmuch as the edema fluid contains a high concentration of protein. The effective colloid osmotic pressure is not measured by the concentration of serum albumin, but by the difference between the concentrations of albumin in serum and ascitic fluid respectively. When serum albumin is given to the patient with ascites, a portion of the albumin finds its way into the peritoneal cavity. The concentration of protein in the latter parallels that of the serum. Consequently, although the colloid osmotic pressure of the serum rises, the difference between serum and ascitic fluid, the effective colloid osmotic pressure, does not.

The question of the edema of heart failure has been deferred until the end of this discourse because of its complexity and the controversy that centers about it. A logical sequence to explain the development of such edema in conformity with the physico-chemical and physiological principles that govern movements and excretion of fluid was proposed by Starling. The initial event in this sequence is venous stasis, which increases capillary pressure, thereby promoting transudation. After this, as was pointed out above, events take the same course that they would take in hypoalbuminemic edema. This is inevitable since the only conceivable cause for edema is a reduction of the difference, effective colloid osmotic pressure—effective hydrostatic pressure in the capillaries (if the lymphatic flow is neglected). It is a matter of indifference whether this is accomplished by reducing the first term or increasing the second. Against the logic of this hypothesis, a theory of “forward failure” has been proposed which almost reverses the course of the Starling sequence (18). In the theory of “forward failure” the primary event is conceived to be failure of the kidneys to excrete salt and water, especially the former. In support of this theory, it is alleged that the volume of blood in heart failure is expanded, not contracted, as the Starling hypothesis requires; and that formation of edema (or rather, retention of salt and water) precedes the appearance of venous congestion. It is impossible in the short time remaining for more than a few remarks on this complex subject. As usual, the controversy is concerned partly with differences of factual observation, partly with differences of interpretation. If retention of salt and water is the primary event in the formation of cardiac edema, some physiological cause for such retention must be found. It has been suggested that renal circulatory disturbances that precede venous congestion are responsible, but such disturbances have not been consistently demonstrated. Renal plasma flow and glomerular filtration may be, but are not regularly, reduced in patients with edema of heart failure. Even if they were, reduction of these functions does not necessarily diminish the excretion of salt and water. Blake and associates (19) have shown that venous congestion of the kidneys diminishes the excretion of salt and water without affecting plasma flow or filtration; but, according to the hypothesis of forward failure, the retention of salt precedes any rise of venous pressure. If the

increase of venous pressure did precede the development of edema, there would be no reason to postulate forward failure. The priority of salt retention has, indeed, been challenged. The precise order of events in such a process is hard to establish. It has been pointed out that, so far as salt and water are concerned, the former appears to have a priority in hypoalbuminemic edema.

The second event in the course of forward failure is an expansion of blood volume as a result of the retention of salt and water. Evidence for such an expansion rests largely on measurements by the dye method, which is unreliable in any case and must be peculiarly unreliable in a condition in which the liver is congested and edematous. Measurements by other methods have not been consistent. It has not been established that accession of edema is regularly associated with hemodilution, diuresis with hemoconcentration. If expansion of the circulating blood volume is the precipitating cause of cardiac edema, further expansion should have a deleterious effect, aggravating the edema. This has not, however, proved to be the case. The alleged beneficial effects of 50 per cent glucose in acute failure and the use of transfusions in the treatment of shock following coronary occlusion are not entirely relevant because these measures are directed toward the correction of secondary vascular reactions rather than failure *per se*. These secondary reactions are undoubtedly accompanied by hemoconcentration. But diuresis has been induced in individual patients with congestive failure by injections of blood, plasma and salt-poor human serum albumin. Even when albumin has not had a diuretic action, in our experience it has had no evil effects. Specifically, it has not increased edema. To hypothecate a condition in which transudation from the blood stream is accelerated, while the volume of fluid in the circulation is expanded, is somewhat anomalous. The agent promoting transudation in this case would have to be increased hydrostatic pressure caused by the expansion, which would constantly tend to restore the volume of circulating blood to normal.

It has been suggested, on the basis of considerable evidence, that the natural reaction to expansion of the blood volume is inhibition of the reabsorption of sodium chloride. It is contraction, not expansion, of the circulating blood to which the kidney usually reacts by accelerating reabsorption of salt. If the blood volume be expanded in cardiac edema, therefore, some reason must be found for the paradoxical response of the kidneys. Such an expansion in any case would involve enlargement of the vascular bed with some change in the distribution of blood within the circulation. It is conceivable that in heart failure a large proportion of the blood may be displaced into the liver or the venous circulation of the extremities in such a manner that the normal receptor is not apprised of the situation. It has been suggested that the blood is diverted from the kidneys in this manner or even by constriction of the renal arteries. If, however, reduction of renal plasma flow and glomerular filtration is not a consistent feature of cardiac edema, such diversion can not be essential for its production.

The sequence of events postulated in the theory of forward heart failure has not been generally verified. Elevated venous pressure is one of the most frequent disturbances encountered in congestive failure. When Reichsman and Grant (20)



induced heart failure in 3 patients with heart disease by withdrawal of digitalis, venous pressure rose considerably before edema appeared. In fact, it rose in all 3, though only 1 developed evident edema. Undoubtedly, increased venous pressure is not the sole cause of edema in all cases; but when it occurs it can not fail to contribute to the formation of edema. Hypoalbuminemia, anemia and local circulatory disturbances may enhance its effect. The reality of the Starling sequence can not be denied. Its every step can be logically inferred from established principles of physical chemistry and physiology. The Starling principle of the formation of edema, upon which it rests, can not be ignored. Before the theory of forward failure can be accepted, it must be tested by and proved compatible with these principles.

These remarks have been made not in a controversial, but in an enquiring spirit. This whole address has been merely an account of the most recent of repeated efforts to integrate the information available about the metabolism of water and salt, the agencies that control exchanges of these substances, and the instruments through which they work, in order to provide criteria which can be applied to clinical problems and to discover fruitful paths for further explorations.

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## THROMBOPHLEBITIS SECONDARY TO ACUTE RESPIRATORY INFECTION\*

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Thrombophlebitis, and thromboembolic disease in general, has been most commonly associated with prolonged immobilization resulting from postoperative or post partum bed rest. Older patients with chronic incapacitating, particularly cardiac disease who often are confined to bed over long periods of time are also apt to develop thromboembolic phenomena. Although the two aforementioned etiologic categories comprise the majority of cases of thromboembolic disease, there are other well recognized causative factors. Thus thrombophlebitis has been causally associated with many specific infectious diseases, such as typhoid fever (11, 30, 32, 34) either as a toxic-allergic reaction or as an actual typhoid suppurative endophlebitis; scarlet fever (12, 17, 23, 32, 34); pneumonia (11, 25), also either toxic or suppurative in the presence of septicemia (25); and even measles (32), mumps (21), and ulcerative colitis (5). The entire field of thrombophlebitis complicating a wide variety of infectious and systemic diseases has been thoroughly reviewed by Nelson Barker (11).

To the foregoing may be added the category of so-called effort thrombosis, another well-defined condition, pathogenetically still somewhat obscure, usually affecting the axillary veins. The etiologic moment of strain, trauma, and sudden effort in this group has been both defended (8, 13, 16, 22) and disputed (26). Those who are in disagreement with this view have pointed to the observation that effort thrombosis occurs only in a vein previously affected by infection or some other disease process (2, 3, 26, 29). Thrombophlebitis following effort or trauma, sometimes only slight in degree, has also been described as occurring in the lower extremities (24), in connection with such minor injuries as twisting or straining the back or twisting ankle or a knee.

The foregoing categories still leave a poorly defined group of instances of so-called idiopathic thrombophlebitis occurring sporadically in young, ambulatory, and presumably healthy people. Occasionally this is a recurrent phenomenon. Barker (6, 7, 9, 10) has reported this subgroup under the name of recurrent idiopathic thrombophlebitis. These patients were (9) "robust, healthy individuals who have not recently undergone operations or had infectious diseases; it occurred without relation to childbirth, injury, local infectious process and in the absence of cardiac decompensation, blood dyscrasia, severe constitutional disease, or previous or associated disease of the veins or arteries." He reported a total of forty such recurrent cases, and although in all of them there was no recognisable evidence of arterial disease, he felt (6) that the lesions were "very similar to those occurring in thromboangiitis obliterans and may possibly represent a form of this disease which is restricted to the veins."

Although usually sporadic, the so-called "primary idiopathic thrombophlebitis" has been reported occurring in epidemic fashion in healthy young adult

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African males (19, 20, 27). Fisher (19) described 21 cases from a copper mining area in Northern Rhodesia and Manson-Bahr and Charters (27) described 627 cases among the Askaris in the East African Command, many of whom had had recent antiluetic therapy. Among these hundreds of cases in natives there were four in Europeans (19, 20). In all of these groups from Africa, the authors were unable to explain the epidemic nature of this disease. Such epidemics have not been reported elsewhere.

Leaving out these unusual epidemic instances in Africa and the recurrent cases which may well represent a *forme fruste* of thromboangiitis obliterans as suggested by Barker, there is left a considerable group of sporadically occurring, single episodes of acute thrombophlebitis in healthy, young, ambulatory adults deserving careful analysis. Welch and Goodhart, both writing in Allbutt and Rolleston's System of Medicine in 1909 (1) called attention to a preceding respiratory infection as being of etiologic importance and stated that "knowledge of thrombosis in influenza dates back to the pandemic of 1889-1890." Welch stressed the "frequency and occasional diagnostic value of this complication which may appear during the course of disease or weeks afterwards and in mild as well as severe cases." Goodhart went so far as to state that "this feature (thrombophlebitis) helped in two or three cases to determine the real nature of an otherwise indeterminate fever." Owen (31) after the subsequent great pandemic of influenza "drew attention to the commonly observed occurrence of venous thrombosis . . . ever since influenza returned in 1918. . . . Thrombotic cases almost invariably occurred when the influenza curves rose and were rarely seen when influenza became scarce."

Since then other authors have called attention to the relationship of idiopathic thrombophlebitis and grippe (3, 14), influenza (4, 28) and pneumonitis (4, 18). Barker (11) in his review of "thrombophlebitis complicating infectious and systemic diseases" also called attention to the cases in such group which follow influenza, acute tonsillitis and pharyngitis. Occasionally an attempt has been made to implicate some other factors such as vaccination (15) and foci of infection in teeth and tonsils (29, 33). However, most often these sporadic cases of thrombophlebitis affect usually the lower extremities and occur in young and presumably healthy people without a history of trauma. Careful investigation in such instances has often elicited a history of an upper respiratory or grippelike infection preceding the phlebitis by two or three weeks.

Despite the fact that the literature is rich in references to the association between mild respiratory infections and thrombophlebitis, little attention is paid to it in general practice. Since three such cases of thrombophlebitis came under observation on the wards of the Mount Sinai Hospital within a short span of time, it was felt worthwhile to report the group.

#### CASE REPORTS

*Case I.* (Mount Sinai Hospital Adm. # 578101). A woman, aged 36 years, Puerto Rican, entered the hospital complaining of a swelling of the left leg of four days duration. Two weeks earlier she suddenly developed generalized aches and pains, malaise, non-productive cough and headache, which confined her to bed for 2 or 3 days. She was then up and about

and apparently well until four days before admission when she was awakened from sleep with severe pain in the left leg. By morning the entire leg was swollen and red and there was a violaceous discoloration over the anterior and mesial aspects of the thigh. The pain and swelling persisted and the leg felt alternately warm and cold. There were no previous similar episodes and no history of trauma, infection in the leg, or gonorrhea. She was pregnant four times, with the last pregnancy two years before. There was no evidence of phlebitis in association with any of the pregnancies. There was no epidermatophytosis.

*Examination.* The only findings were those noted in the affected extremity. There was a slight elevation of temperature 100.6°F., pulse 70, and the blood pressure was 100 systolic and 60 diastolic. The head and neck were normal. The lungs were clear and the heart was normal. The abdomen was negative except for marked tenderness on deep pressure in the left lower quadrant immediately above the inguinal ligament. The entire left lower extremity was markedly tender, swollen, tense, somewhat warmer than the other particularly in the calf which was somewhat reddened. There was tenderness but no palpable cords in the posterior calf and over the course of the saphenous, femoral, and iliac veins. Homan's sign was positive. The left thigh was two inches larger than the right and the left calf an inch and a half larger than the right. Arterial pulsations were all normal.

The neurologic status was negative. Pelvic and rectal examinations revealed no significant findings. There was no evidence of trauma or dermatophytosis.

*Laboratory data.* The hemoglobin, 13 Gm.; White blood count, 7,450 with a normal count differential. The urinalysis was negative except for one plus albuminuria noted on admission which subsequently disappeared. Sedimentation rate was 65 mm. per hour (Westergren). The blood urea and sugar were normal and the blood Wassermann test was negative. Fluoroscopy of the heart and the lungs disclosed no abnormalities. A gynecologic consultant found no pelvic cause for the thrombophlebitis.

*Course:* The diagnosis was that of an acute deep vein thrombophlebitis of the left leg following a flu-like syndrome. The patient was placed on dicumarol with the prothrombin time being kept at a level between 23 and 34 seconds (control of 11-13). After three days of treatment there was apparent marked improvement and at the end of three weeks complete subsidence of all signs, except for some residual tenderness over the calf and along the course of the saphenous and femoral veins. She left the hospital on the 21st hospital day.

*Case 2. History* (Mount Sinai Hospital Adm. #577341). A colored man, aged 23 years, entered the hospital complaining of cramp-like pain in the left calf, worse on weight bearing, of five days duration. Two and a half weeks earlier he developed the "grippe" with low grade fever, slight dyspnea, and cough which kept him in bed for three days. Two weeks later he began to experience pain in the left calf. There was no history of trauma. Eight months before he had had an acute gonorrheal urethritis which had been treated with penicillin. Cure had been completed and there was no persistence of urethral discharge.

*Examination.* The positive findings were limited to the left leg. Temperature was 100.8°F.; pulse was 84; blood pressure was 106 systolic and 80 diastolic. The lungs were clear, the heart normal, and the abdomen negative. The left calf had a three quarter inch larger circumference than the right. There was tenderness over the entire calf, in the popliteal space and in the lower part of the medial aspect of the thigh. Homan's sign was positive on the left. Arterial pulsations were all adequate.

Neurologic status was negative. The prostate was normal and no secretion could be expressed. The left knee was held in partial flexion, due to involvement of veins in popliteal space, but was not swollen.

*Laboratory data.* Hemoglobin, 16 Gm.; White blood count, 7,500 with normal differential count. The urine was normal; the stool Guaiac test was negative. Sedimentation rate was 14 mm. per hour (Westergren). The blood urea, sugar and total protein were normal and the blood Wassermann test was negative. Urine concentration test, specific gravity up to 1.032 and the PSP (phenolsulfonphthalein) excretion was 70% in two hours. The Mantoux was negative in dilution of 1:100. X-Ray examination of the chest was negative and that of the bones of left leg showed no evidence of periostitis or any other abnormality.



*Course:* The diagnosis was that of acute deep vein thrombophlebitis of the left leg secondary to the "grippe"-like syndrome two weeks before. Shortly after admission left para-vertebral novocaine block was done with marked relief of pain and tenderness and increased warmth in the leg. Relief however was short lived and the patient was then placed on dicumarol, with the prothrombin time being maintained at a level of between 23 and 30 seconds (controls of 11 to 13). Over a three week period there was gradual subsidence of the pain, tenderness, warmth, and swelling and the Homan's sign disappeared. The patient was discharged on the 24th hospital day. On follow-up examination, eight months later, he still complained of occasional edema of the leg on prolonged standing, but otherwise was apparently well.

*Case 3. History.* (Mount Sinai Hospital Adm. #587451). A white boy, aged 16 years, entered the hospital complaining of pain in the right calf, heaviness in the chest and dyspnea of three weeks' duration. The onset was sudden with a cramp in his right thigh which became progressively worse and was soon followed by painful swelling of the ankle, calf, and thigh. This was accompanied by fever to 103°F. and chills. There was no response to sulfa\* and penicillin. Investigation in another hospital, two weeks before entering the Mount Sinai Hospital, revealed inflamed nasopharynx and ear drums. There was an area of increased density in the right lower lobe, disclosed on X-Ray examination of the chest. This was thought to be a pneumonic process. The right leg displayed painful swelling at the ankle, calf and thigh. The white blood count was 7,200 with 52% polymorphonuclears and 48% lymphocytes.

The fever, leg pains, and a sense of heaviness in the chest aggravated by respiration continued up until his transfer to the Mount Sinai Hospital. Repeat chest film just before the transfer showed complete resolution of the infiltration previously seen. There was no hemoptysis at any time. There was no history of trauma or gonorrhea.

*Examination.* The temperature was 100.2°F., pulse 90; and blood pressure, 118 systolic and 64 diastolic. The head and neck were negative except for injected nasal mucosa. The fundi were normal. There were a few pea-sized discrete postcervical and inguinal nodes. The lungs were clear and the heart normal. The abdomen showed an appendectomy scar. Rectal examination was negative. The right leg showed a thickened, tender right saphenous vein in the thigh with shotty femoral nodes. The edema and calf tenderness previously present had all subsided. Homan's sign was negative.

*Laboratory data:* Hemoglobin, 14.5 Gm.; white blood count, 12,400 with 37% polymorphonuclears, 37% lymphocytes, and 26% eosinophiles. The eosinophile count later dropped to 3% and 6%. Platelets were adequate. Urine showed a specific gravity of 1.032, was negative for albumin and on microscopic study. Sedimentation rate was 6 mm. per hour (Westergren). The blood urea and sugar were normal and the blood Wassermann test was negative. X-Ray examination of the chest was negative and an electrocardiogram showed only sinus arrhythmia. The cold agglutinin titer was not elevated. Oscillometries were normal in both legs. Skin tests against crystalline penicillin G (both immediate and delayed 24-48 hrs.), procaine penicillin, and trichophytin were all negative. Trichina precipitin test was a faint doubtful positive. Cold pressor test showed a rise from 118 systolic and 78 diastolic to a maximum of 142 systolic and 84 diastolic. Histamine test disclosed a rise from 120 systolic and 68 diastolic to a maximum of 130 systolic and 82 diastolic.

*Course:* The diagnosis was that of an acute thrombophlebitis of the right leg. To what extent the coincident pneumonitis found at the time of initial examination actually antedated the onset of the phlebitis could not be determined. The marked eosinophilia raised the possibility that the phlebitis was merely a single manifestation of a more diffuse vascular disorder, such as periarteritis nodosa. No other evidence for this diagnosis could be discovered. The fundi were normal. Daily blood pressure readings ranged from 126 systolic and 68 diastolic to 140 systolic and 72 diastolic with a single high of 140 systolic and 88 diastolic. The urinalysis was negative, hemoglobin and sedimentation rate were normal. The

\* The exact sulfa drug used is unknown.



electrocardiogram was normal. The eosinophilia gradually subsided. It has not been present when the patient was first seen in the other hospital. It was felt that it might well represent an allergic response to the chemotherapeutic agents that had been employed elsewhere prior to his Mount Sinai admission, though penicillin skin tests were all negative.

The patient ran a low-grade fever for more than a week. The pain in the right thigh gradually disappeared as did the other symptoms. He was discharged on the 13th hospital day. Shortly after his return home there was recurrence of pain in the right thigh and an appearance of pain in the left foot and knee, with redness and swelling over the dorsolateral aspect of the left foot. There developed a slight non-productive cough but no hemoptysis. His temperature rose to 100° F. He received no chemotherapy at this time, and was readmitted to the hospital 60 days later.

*Examination* on the second admission disclosed only slight tenderness over the posterior medial aspect of the right thigh, medial aspect left knee, and lateral aspect of the left ankle together with a small area of purplish discoloration over the dorsolateral aspect of the left foot. The laboratory investigation revealed no new findings. Eosinophile counts were 10%, 4%, 4%.

A probable relapse of thrombophlebitis secondary to a pneumonic infection or phlebitis as a manifestation of a generalized vascular disorder were again considered in the differential diagnosis. This time again conservative management implemented with physiotherapy was followed by a subsidence of all complaints and the patient was discharged on the 15th hospital day.

#### DISCUSSION

Of the small herein described group of patients, Cases 1 and 2 fit readily into the category of acute thrombophlebitis occurring in young, healthy, active people, and developing some two to three weeks after a preceding relatively mild respiratory infection. They emphasize that too little attention is paid to the causal relationship of acute thrombophlebitis to a preceding acute non-specific respiratory infection.

The third case (Case 3) raises a problem of greater complexity. The associated eosinophilia, not entirely adequately explained as due to drug allergy, suggested the possibility of diffuse vascular disease (periarteritis nodosa). No supporting evidence for this suspicion could, however, be found. The recurrence of the thrombophlebitis and its appearance also in the contralateral extremity also raised the possibility that this case might fall in the category of recurrent idiopathic thrombophlebitis of the type described by Barker who felt that it might possibly be the precursor of or a *forme fruste* of thromboangiitis obliterans limited at this time at least, entirely to the venous side of the vascular bed.

The three cases together illustrate the relatively frequent occurrence of acute thrombophlebitis in young, healthy, ambulatory people and some of the problems in diagnosis and management that they raise. They lend additional support to the concept that in these cases the thrombophlebitis is causally related to a preceding respiratory infection.

#### SUMMARY

1. The literature on the subject of thrombophlebitis in healthy, ambulatory young people is reviewed. The probable relationship of this affection to preceding respiratory tract infection is reemphasized.

2. Three cases are presented to illustrate the not rare occurrence of this syndrome and to emphasize some of the problems in differential diagnosis.

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## GALLSTONE OBSTRUCTION OF THE DUODENUM: CASE REPORT\*

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Mechanical intestinal obstruction by a biliary calculus is not an uncommon occurrence. Bennett (1) analyzed 3064 cases of intestinal obstruction 0.9% of which were caused by gallstone. Souttar (2) reported an incidence of 1.7% in 1655 cases, while Vick (3) in a study of 3625 cases reported 1.3% as caused by gallstone. More recently, Baleh (4) in a review of all cases of intestinal obstruction admitted to the Massachusetts General Hospital in Boston between 1898 and 1932, stated that 2.0% were caused by obstructing biliary calculus. It has been the experience of these authors that obstruction of the intestine most commonly occurs in the lower ileum. Obstruction of the duodenum, however, is rarely seen. Perhaps the most comprehensive report was presented by Hertz (5) who carefully reviewed the literature up to and including 1947 and found only 35 cases of gallstone impaction as a direct cause of obstruction of the duodenum. Two cases not included in that review were reported in 1939 by Dulin and Peterson (6), and one additional case appeared in the literature in 1950 (7) making a total of 39 including the present case report.

Fistula between the gallbladder and gastrointestinal tract is by no means a rarity, and is frequently found during the course of biliary surgery. Cholecysto-enteric fistula is most commonly found between the gallbladder and duodenum (8, 9, 10). Anatomically the path taken by a biliary fistula is not limited. Gallstones have been vomited from the stomach, coughed from the bronchial tree, voided in the urine and frequently passed per rectum. Fistulous tracts have been discovered between the gall-bladder and duodenum, stomach, jejunum, ileum, colon and appendix; between the gallbladder and the common and hepatic ducts, and the liver. They have been traced to the genito-urinary system as well. Internal biliary fistulae are most frequently caused by gallstones. Perforating duodenal ulcers constitute the second most important cause, while neoplastic growths constitute only an occasional factor in the etiology of such a condition (11). The intimate anatomical relationship between the gallbladder, especially when distended, and the second portion of the duodenum, probably accounts for the greater frequency of fistula between these two organs. The usual pathologic sequence of events is cholelithiasis, acute cholecystitis, pericholecystitis and the formation of adhesions between the gallbladder and adjacent organs. Ulceration of the wall of the gallbladder then occurs with perforation subsequently into an adjoining organ by pressure necrosis thereby forming an internal biliary fistula.

### CASE REPORT

*History:* Mount Sinai Hospital adm. #604073. P. R., aged 67 years, a housewife, was admitted nine months prior to admission to The Mount Sinai Hospital, to another hospital

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complaining of severe right upper quadrant abdominal pain, nausea and vomiting, and icterus developed shortly thereafter. On conservative therapy, all symptoms subsided and the patient was discharged after two weeks of hospitalization. She remained asymptomatic until nine days before admission to The Mount Sinai Hospital. At that time she suddenly developed persistent nausea and vomiting, constipation but no abdominal pain. There was no history of fatty food intolerance, previous bowel habit disturbance, melena or abdominal distention. Because of the persistence of symptoms and increasing dehydration, she was hospitalized at the institution previously entered. Physical examination revealed an obese acutely ill woman whose tongue and skin were dry. The abdomen was obese, not distended and non-tender, and no masses were palpated.

*Laboratory data:* the hemoglobin was 85%; red blood cell count, 4,280,000; white blood cell count, 16,300; segmented polys, 70, non-segmented polys, 1, lymphocytes 29. Urinary-



FIG. 1. X-ray of upper gastrointestinal tract showing cholecysto-duodenal fistula and gallstone impacted in the third portion of the duodenum.

sis: acid reaction; specific gravity, 1.022; sugar 1 plus; acetone negative; microscopic, 5-8 white blood cells per high power field. Blood Chemistries: Mazzini, negative; total protein, 6.7; albumen, 3.9; globulin, 2.8; blood urea nitrogen, 17.5 mg. per cent; uric acid, 4.7 mg. per cent; phosphorus, 3.3 mg. per cent; alkaline phosphatase, 8.6 Bodansky Units; CO<sub>2</sub> combining power 98.2 Vol. per cent; chlorides, 282 mg. per cent; bilirubin, 0.8 mg. per cent. No blood sugar level was recorded.

*Electrocardiogram* revealed evidence of coronary insufficiency.

*X-ray:* Abdominal scout film, chest film, and barium enema were essentially negative. Examination of the upper gastrointestinal tract demonstrated passage of barium from the pyloroduodenal area towards the gallbladder region, presumably through a fistulous tract. There appeared to be a large mass impacted in the third portion of the duodenum outlined by the barium and obstructing the lumen (fig. 1).

The patient's electrolyte balance was restored by supportive therapy and immediate surgery was advised. The patient elected to transfer to The Mount Sinai Hospital for operation.

On admission it was learned that no stool had been passed per rectum for nine days.

Further questioning revealed that the patient had been a known diabetic for twelve years requiring protamine zinc insulin, 20 units daily. Blood sugar determinations varied widely ranging between 125 mg. per 100 cc. and 273 mg. per 100 cc., and no diet of any kind had been adhered to. All insulin had been discontinued at the onset of the illness.

*Examination* revealed a well-developed obese woman who did not appear acutely ill, dehydrated, or in any discomfort. The abdomen was not distended or tender and no masses were palpated. The rectum contained stool which was brown. The remainder of the examination was essentially negative.

*Laboratory Data:* The hemoglobin was 11.0 gm; red blood cell count, 3,820,000; white blood cell count, 9400; differential smear, normal. Urinalysis: Alkaline reaction; specific gravity, 1.014; albumen, a trace; sugar, negative; acetone, negative; microscopic, many white blood cells with clumping, occasional red blood cell (note: uneatheterized specimen).

*Electrocardiogram* was normal.

*Course:* The patient received erycicillin 300,000 units twice daily and streptomycin 2.0 Gm. daily. On admission the temperature was 100.6 F. and remained at about this level during the preoperative period. Blood sugars were determined on two successive days and found to be 165 mg. per cent and 145 mg. per cent respectively. No insulin was being given during this time. Blood urea nitrogen and total protein determinations were found to be essentially the same as that found in the other hospital. On the day after admission a bland low fat diet was tolerated without distress. Five days after admission she was subjected to surgical intervention.

*Operation:* Under gas-oxygen-ether anaesthesia the peritoneal cavity was entered through an upper right rectus muscle splitting incision. Numerous adhesions were encountered between the gallbladder and stomach and duodenum. These were separated and a thickened atrophic gallbladder was visualized with a fistulous tract extending from it to the first portion of the duodenum. A large gallstone the size of a golf ball was palpated in the third portion of the duodenum. The liver and pancreas were normal. The gallbladder was dissected free of the duodenum, the fistulous tract excised, and the fistulous opening in the duodenum closed in two layers. The gallbladder was then removed from above downward, the cystic artery and cystic duct being ligated individually. The common duct was opened, explored and a moderate amount of debris removed. Successively larger dilators were passed into the duodenum easily, the duct irrigated through a catheter, and then closed about a t-tube. The third portion of the duodenum was then mobilized and incised longitudinally over the stone. After delivering the stone, the duodenum was closed transversely in two layers. One penrose drain was placed in the retroduodenal space, and two similar drains were inserted in the sub-hepatic space of Morrison. The abdominal wall was approximated with interrupted buried figure-of-eight steel wire and the skin was closed with michel clips.

*Post-operative course:* Convalescence was uneventful and except on two occasions, no insulin was given. A soft diet was well tolerated four days after surgery and fractional urine specimens remained free of sugar and acetone until discharge. A cholangiogram on the tenth post-operative day demonstrated a common bile duct which was dilated but no delay in the passage of opaque medium into the duodenum was observed. Because of the dilated common duct and because of moderate discomfort following clamping of the t-tube for a twenty-four period, the patient was discharged with the t-tube *in situ*. This was removed on the thirteenth post-operative day.

*Follow-up studies:* The patient was well two months after operation. Blood sugar 185 mg. per cent was reported one month after discharge, the urine remains sugar-free, and no insulin has been administered. The patient has adhered to a modified diabetic diet and feels entirely well.

#### DISCUSSION

The possibility of a relationship between Diabetes Mellitus and gallbladder disease has been a matter of discussion for many years. Considerable material ap-

peared in the literature in the pre-insulin era attempting to establish the postulate that eradication of the diseased gallbladder will either cure or decrease the severity of the diabetes. This has been disproved by many workers in the field, but notably by Eisele (12) who studied a group of seventy-six diabetic patients undergoing surgery of the biliary system with complications including hydrops, empyema, gangrene, perforation, pancreatitis, and rupture of some portion of the biliary tree by a calculus. The diabetic status as measured by the insulin requirement one year before and one year after surgery in the average case was unchanged. It was also established in this report that the presence or absence of jaundice does not affect the severity of the diabetes subsequent to successful surgery.

The apparent improvement in the diabetic status of the patient whose case is presented cannot be said to be the result of the surgery performed since the insulin requirement was diminished preoperatively. Furthermore, since operation, the patient has been on a diet prescribed by her physician and thus the need for insulin is not as great as formerly.

#### SUMMARY

A case of obstruction of the third portion of the duodenum by a biliary calculus with an associated cholecystoduodenal fistula is presented and discussed. The literature is briefly reviewed and the number of cases reported to date is tabulated.

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# CASE OF COEXISTENT BENIGN AND MALIGNANT BONE TUMORS\*, \*\*

JACOB F. KATZ, M.D., AND FREDERICK M. MAREK, M.D.

## CASE REPORT

*History.* (Admission #596464) C. R., a Puerto Rican man, aged 19 years, was admitted to The Mount Sinai Hospital on May 17, 1949 for pain and swelling of the right knee. He was apparently well until 3 months before admission when he first noted pain in the right knee and lower thigh, which gradually increased in severity and became associated with a limp. Six weeks later, he noted a mass in the lower portion of the thigh, which increased rapidly in size. No history of injury was elicited.

*Examination.* The general physical examination was negative. Local inspection of the right lower extremity revealed the following: A firm, rounded swelling  $5\frac{1}{2}$  inches in diameter present over the medial aspect of the lower third of the right thigh. There was slight local heat. Tenderness was minimal over the major portion of the tumor but exquisite at the postero-medial margin near the joint line. The skin was freely movable over the tumor but the tumor itself was firmly fixed to the deeper tissues. The circumference of the right thigh at the summit of the tumor was  $1\frac{1}{2}$  inches greater than the unaffected left thigh.

The right knee joint did not seem involved, but motion was mechanically restricted by the mass in the lower right thigh. The joint could be extended to 170 degrees and flexed to 60 degrees. Many firm nodes of varying size, not tender, were palpable in the right groin. The patient walked with a slight limp favoring the right lower extremity.

*Laboratory Data.* The hemoglobin was 14.2 grams; white blood count, 6550 with a normal differential; sedimentation rate (Westergren), 15 mm per hour; urinalysis, negative. The tuberculin test was positive in a dilution of 1:10,000; Kahn test was negative. Chemical studies showed serum calcium to be 11.6 mg. per cent and phosphorus, 2.4 mg. per cent; alkaline phosphatase was 14 K.A. units; total serum protein was 7 grams.

*X-ray examination* (fig. 1) of the right thigh was reported as follows: "On the postero-medial aspect of the femur at the region of the proximal part of its distal third, there is an irregular area of diminished density, measuring 3 x 4 centimeters. In several of the available films, there appear to be a number of small, circular, radiolucent regions within this area. However, other films give the impression that there is an irregularly contoured cavity-like structure which is responsible for the appearance. Peripherally, the area is demarcated by a narrow zone of dense bone which is irregular in outline. Distal to this site, and extending on the medial aspect of the femur to within an inch of the articular margin of the medial condyle, is a zone of diminished density. Within the latter, the trabeculae appear to be, in some areas, destroyed and the overlying cortex is irregularly thinned. At the supero-medial aspect of the medial condyle, there is apparent destruction of the cortex with a fragment of osseous tissue lying free in the adjacent soft tissues at least  $\frac{1}{4}$  inch removed from the condyle. Soft tissue swelling is present over this region. I believe that the proximal lesion is benign, in the nature of a chondroma or a fibroma, and that a portion of this has undergone a malignant change which has spread distally to involve a portion of the medial condyle with subsequent destruction and penetration of the overlying cortex in the latter region and invasion of the neighboring soft tissues. X-ray examination of the chest was negative."

*Course.* The clinical impression was that of a malignant bone tumor, probably an osteogenic sarcoma. The possibility of malignant degeneration of a preexisting benign tumor, such as fibroma or giant cell tumor, was considered.

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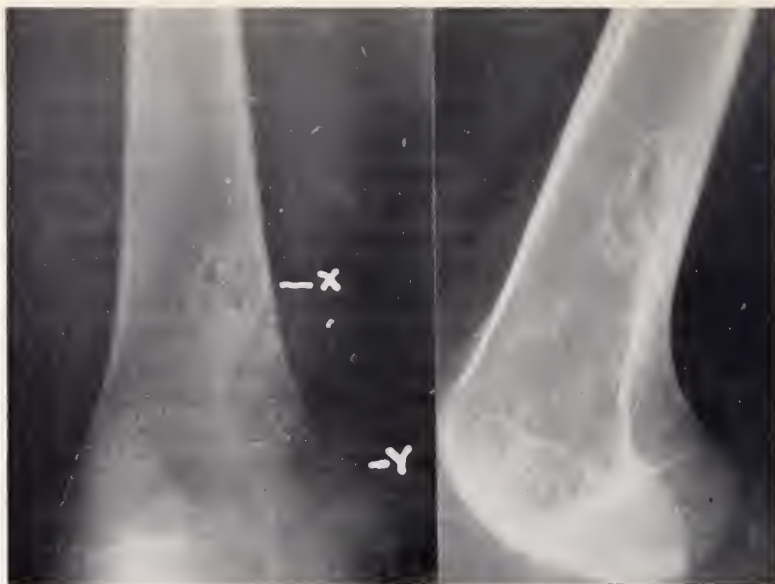


FIG. 1. A, A-P and B, lateral views of lower end of right femur, showing a well circumscribed benign (x) lesion at the postero-medial aspect of lower shaft. Distal to this, there is a destructive lesion (y) with an adjacent soft tissue tumor.

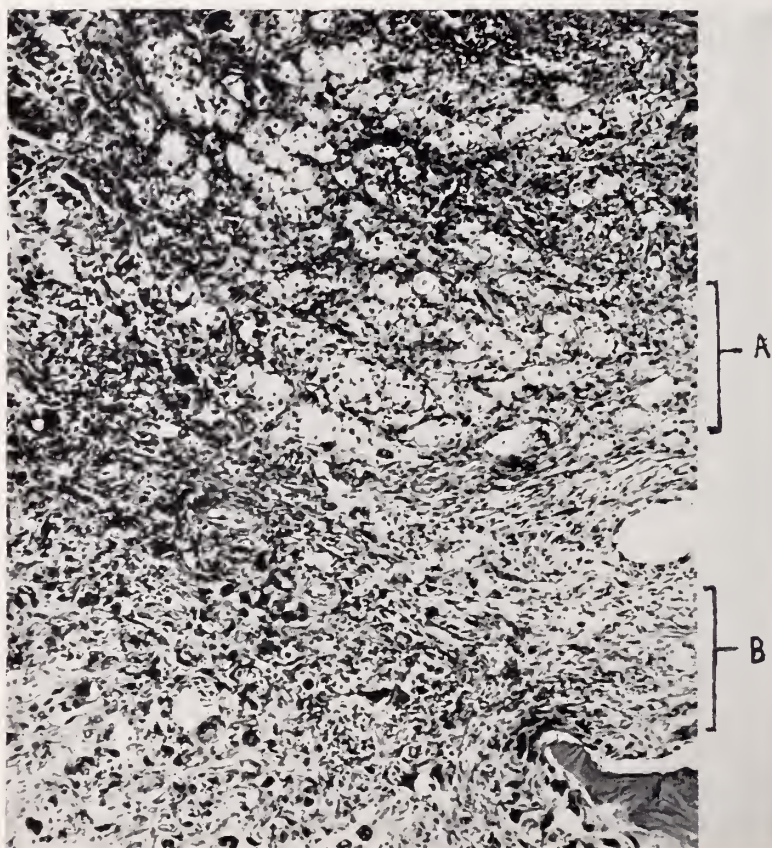


FIG. 2. Low power field ( $\times 100$ ) showing the foam cells in the fibroma (A), with bordering invading malignant cells (B).

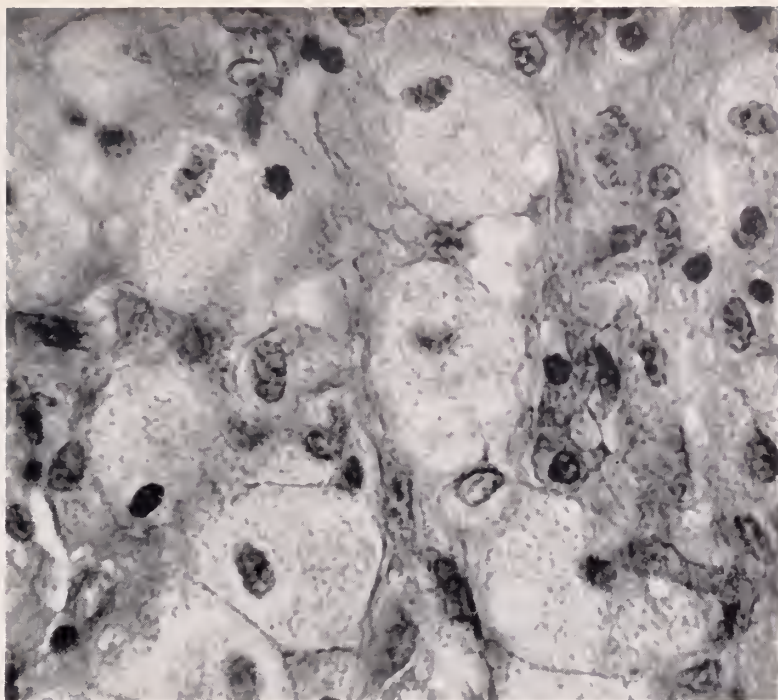


FIG. 3. High magnification ( $\times 1500$ ) of the typical foam cells or lipophages demonstrating the orderly benign morphology, shown in figure 2 at A.

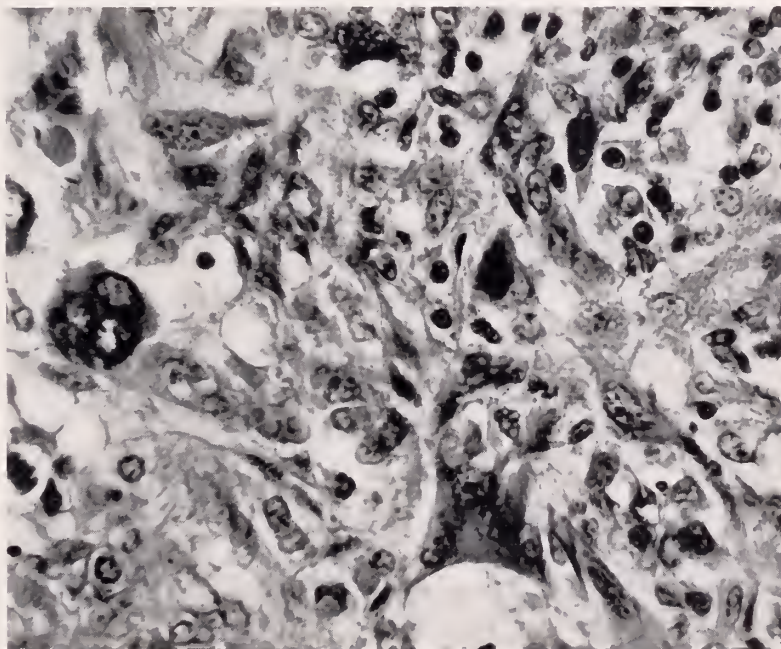


FIG. 4. High magnification ( $\times 650$ ) of the invading malignant zone (fig. 2 at B) demonstrating multinucleated cells, polymorphism and mitotic figures.



On May 28, 1949, under general anesthesia, through a small medial incision, biopsy of the tumor was performed. Homogenous gray tumor tissue was removed for histological study. The pathological report was that of osteogenic sarcoma. Pre-operative radiation was not considered indicated by the radiotherapist. On June 4, 1949, under general anesthesia, with preliminary ligation of the femoral artery above its profunda branch, a high thigh amputation was done. No tumor tissue was observed grossly at the level of amputation. Several large inguinal nodes were removed for pathological investigation.

*Pathological studies* of the amputated lower extremity revealed the following: "The amputated femoral segment measured 25 centimeters. A poorly circumscribed neoplasm, measuring 8 x 5 centimeters, extended to within 1½ centimeters of the distal articular surface of the femur. Half of the tumor extended beyond the original medial cortex. The tumor tissue was friable, granular, diffusely hemorrhagic, with focal yellow areas in the extra-periosteal portion. The neoplasm invaded the adjacent skeletal muscle. Just superior to the main neoplastic mass, there was a sharply delimited, irregularly shaped, soft, yellow nodule, measuring one centimeter in diameter."

Microscopic study (figs. 2, 3 and 4) of the neoplastic tissues revealed an osteolytic osteogenic sarcoma (figs. 2 at B and 4) upon which bordered a fibroma containing nests of xanthoma cells (figs. 2 at A and 3). There was no pathological evidence of clear cut malignant degeneration of the fibroma. Microscopic examination of the lymph nodes revealed sinus endothelial hyperplasia in which no tumor cells were present. The sections of tissue were examined independently by several pathologists who concurred in this interpretation.

The post-operative course was uneventful. The patient left the hospital on June 17, 1949, and subsequently was observed in the out-patient department where he was fitted with a satisfactory prosthesis. Six months later (January 1950), pulmonary metastases were discovered on follow-up chest X-ray examination.

#### SUMMARY

Although X-ray examination suggested malignant degeneration of a benign bone lesion, pathological study revealed two separate entities in which the benign fibroma retained its characteristic histology and delineation. The case which has been presented remains distinctive in the unusual association in close proximity of a benign fibroma of bone with an osteogenic sarcoma.

A thorough review of the literature disclosed no record of benign and malignant bone tumors occurring in close proximity to one another in a single bone. Malignant transformation of primarily benign lesions such as Paget's disease with associated osteogenic sarcoma (1, 2) has been cited with increasing frequency. Instances of bone sarcoma have also been reported to occur with fragilitas ossium (3), polyostotic fibrous dysplasia (4) and diaphysial aclasis (5). Coley, commenting on the pathogenesis of osteogenic sarcoma (6), stated "that the possibility that osteogenic sarcoma, chondrosarcoma, or fibrosarcoma may be engrafted upon a wide variety of bone lesions which are of themselves benign, should always be borne in mind. Some of these are not at all uncommon, e.g. Paget's disease of bone, chondroma, and giant cell tumor. Many, however, are conditions which are of themselves relatively rare. Among these may be mentioned fibrous dysplasia, osteopetrosis, and ossifying hematoma, in all of which sarcomatous change has either been reported or observed." Geschickter and Copeland (7) mention one case of benign giant cell tumor and another case of fibrous dysplasia which preceded development of osteolytic sarcoma at the same sites. Jaffe and Lichtenstein (8) in their report on non-osteogenic fibroma of bone

stressed the benignancy of this lesion, its predilection for adolescents, and a histopathology often characterized by nests of lipoid-containing foam cells. In one of their cases in which the fibroma was in the tibia, the lesion was discovered incidentally to X-ray examination of the femur for an osteogenic sarcoma.

Because of the rarity of the co-existence of a benign fibroma and a highly destructive osteogenic sarcoma in juxtaposition within a single bone, this case is reported.

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## THE MOUTH IN DIABETES MELLITUS\*

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Diabetes mellitus is a chronic disease syndrome which is known to influence many tissues and organs in the body. Prior to 1921 a great many diabetics did not survive long enough to develop chronic changes. This was especially true of the children and adolescents who died early in the course of their disease. After the introduction of insulin, these people were enabled to live. It is of extreme importance to know whether insulin while adding to longevity, also prevented the development of changes in other tissues and organs. This report deals with the occurrence of oral changes in 149 patients who have had diabetes over a period of time. A search was made for any specific oral lesions associated with this disease syndrome; and an attempt was made to correlate the state of the oral tissues with the degree and type of diabetic control.

### METHODS

Patients were selected at random from the clinic population. Their diabetic status was unknown to the examiner at the time of oral examination. The following procedures were used; interrogation; clinical inspection and examination; full series intraoral roentgenographic studies; preliminary long bone roentgenographic studies; blood Vitamin A and Carotene determinations.

**INTERROGATION.** Patients were asked whether they had any remarks or complaints to make concerning their oral condition, and these were noted. Where tooth loss had occurred, an attempt was made to elicit reason for same, and time of loss.

**CLINICAL INSPECTION AND EXAMINATION.** This was performed, using a Castle Examining Light for illumination and tongue blades, mouth mirrors and explorers.

The following tissues were carefully examined and, wherever possible, changes were graded from 1 through 4 in increasing severity.

- a. *Lips:* external and mucosal surfaces, vermillion border, angle of mouth. For color, presence of old scars, fresh granulations, fissures, scaling, areas of denudation.
- b. *Oral mucosa:* floor of mouth, muco-buccal folds, buccal parietes. For color, ulcerations, appearance of vessels at surface.
- c. *Hard and soft palates:* for color, ulcerations, appearance of vessels at surface of soft palate.
- d. *Tongue:* for color, size, form, topography, atrophy or hypertrophy of papillae, ulceration, coating.

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e. *Gingivae*: interdental papillae, marginal, cemental. For color, texture, bleeding, hypertrophy, recession, pus, pockets, abscess formation, polyps.

f. *Teeth*: for caries, erosions, mobility, restorations.

Items not mentioned above were recorded as miscellaneous findings.

**ROENTGENOGRAMS.** Full series intra-oral roentgenograms were obtained in 120 cases. Conditions present were noted. In dentulous patients alveolar bone loss was graded 1 through 4 in increasing severity. Ten individuals who manifested severe alveolar bone loss were chosen for preliminary study of the rest of the skeleton, roentgenograms of the hands and femora were made.

**VITAMIN A AND CAROTENE DETERMINATIONS.** Twenty-two patients who exhibited a yellow coloration of the soft tissues of the mouth, or hyperkeratinization of gingivae or oral mucosa, or leukoplakia, or Fordyce's granules were chosen for fasting serum Vitamin A and carotene determinations. Twenty-one patients who exhibited no changes of the above nature were selected for control determinations.

#### COMMENT

*Distribution of Cases.* The accompanying table (table I) shows that 81 per cent of the group were between the ages of 41 and 70, and that 67 per cent of the group were female. This is a representative sample of our clinic population.

*Incidence of Patients' Subjective Symptoms.* See table II.

**NATURE OF SUBJECTIVE SYMPTOMS.** Tables II and III show that 36 per cent of the group presented such subjective complaints as denture irritation, dryness of the mouth, loose and painful teeth, burning lips, tongue, and palate, receding, bleeding and painful gums. In addition to these we can add from records of other diabetics, not included in this tabulation, tenderness at the temporo-mandibular joint, loose and poorly fitting dentures, bad mouth odors, swelling in the parotid region, chapped lips, and abscess formation. It would be difficult to designate any of the above as being typical of diabetic individuals since they occur in non-diabetics as well. We have no figures to indicate the relative frequency of occurrence in diabetics and non-diabetics. It would also be interesting to compare the above with what one experiences in poorly controlled diabetics. A survey of such individuals, choosing newly diagnosed and untreated cases is now under way in our clinic.

**INCIDENCE AND NATURE OF TISSUE CHANGES.** The majority of tissue changes noted and listed in table IV (2), are often associated with nutritional and metabolic disorders, i.e. indentation, fissuring, fraying, lobulation of the tongue, and hypertrophy of the papillae; also scarring, scaling, fissuring, denudation, and occurrence of granulations on the lips, and the presence of a prominent line of demarcation at the vermilion border; for the gingivae the following changes; edema, recession, hypertrophy, bleeding, pus formation, pocket formation, and incidence of polyps. It should be remembered that local mechanical factors may play an important role in the etiology of many of these changes.

The most prominent change was hypertrophy of filiform papillae of the tongue, of which there were 105 instances of moderate degree and 35 of severe degree.

TABLE I  
*Distribution of Cases*

## 1. According to sex

	NUMBER	PER CENT
Male.....	49	33
Female.....	100	67

## 2. According to age

AGE RANGE	NUMBER	PER CENT
Below 20 yrs.....	5	3
Between 21-30.....	5	3
Between 31-40.....	10	7
Between 41-50.....	15	10
Between 51-60.....	57	38
Between 61-70.....	48	33
Between 71-80.....	9	6

TABLE II  
*Incidence of Patients' Subjective Symptoms*

	NUMBER	PER CENT
Present.....	53	36
Absent.....	96	64

TABLE III  
*Nature of Subjective Symptoms*

COMPLAINT	NUMBER
Dryness.....	4
Irritation beneath denture.....	19
Loose teeth.....	3
Painful teeth.....	3
Burning lips.....	6
Burning tongue.....	7
Burning palate.....	2
Receding gingivae.....	1
Bleeding gingivae.....	8
Painful gingivae.....	8
Pus from gingivae.....	1
Swollen cheek	1 each
Pain, blistered lips	
Pain, side of tongue	
Roughness, ext. lip surf.....	
Bleeding from tongue	
Pain, cheek	

TABLE IV  
(1) *Incidence of Tissue Changes*

	NUMBER	PER CENT
Total number of patients with tissue changes.	118	79
1. Number with lip changes.....	65	44
2. Number with tongue changes.....	140	94
3. Number with gingival changes .....	81	54

(2) *Details of Tissue Changes*

	MODERATE NUMBER	SEVERE NUMBER
A. The tongue		
1. Indentation.....	2	
2. Fissuring.....	34	13
3. Fraying.....	1	2
4. Lobulation.....	3	1
5. Hypertrophy Fungiiform pap.....	23	15
Filiform pap.....	105	35
6. Atrophy Fungiiform pap.....	8	6
Filiform pap.....	8	22
B. The Lips		
Fresh granulations.....	8	9
Fissuring.....	13	—
1. Angles old scars.....	1	10
2. Vermillion scaling.....	12	—
Borderline of demarcation.....	6	3
3. External Scaling.....	27	4
Surface Fissuring.....	14	1
4. Mucosal Denudation.....	3	
Surface Mucous gl. enlargement.....	18	
Hyperkeratinization.....	2	
Aphthous ulcers.....	3	
C. The Gingivae (71 dentulous patients)		
1. Edema Cemental gingivae.....	34	22
Interdental pap.....	32	21
2. Recession C.G.....	28	14
I.P.....	16	8
3. Hypertrophy C.G.....	1	1
I.P.....	2	2
4. Bleeding C.G.....	26	8
I.P.....	20	7
5. Pus C.G.....	9	4
I.P.....	8	3
6. Pockets C.G.....	31	21
I.P.....	22	26
7. Polyps C.G.....	2	
I.P.....	1	



Next in frequency of occurrence were gingival edema, fissuring of the tongue, pocket formation about the teeth, recession of the gingivae, bleeding gingivae, and scaling and fissuring of the external lip surfaces. The incidence of pus and polyp formation, it will be seen, were considerably less. The incidence of acute infections was very low; in the past one and a half years only one patient required emergency treatment (for a pericoronitis about a lower third molar.)

The above findings are in agreement with other surveys published since 1940. A review of the literature of the pre-insulin, crystalline insulin, and protamine-zinc insulin eras reveals some interesting changes in the oral tissues of diabetics.

Zilz, in 1915, reported a survey of 100 diabetics (1) which disclosed that in almost all cases subgingival calculus, gingival inflammation, pocket formation, necrosis and resorption of the alveolar process and pus formation were present. Williams, in 1928 (2) felt that the "modifications of pyorrhoea and gingivitis in the diabetic, when closely studied are so nearly constant as to constitute a definite clinical entity." He recognized two classes of diabetics, viz., Class I—well developed diabetes was present but patients had had no treatment. Teeth were loose, gums hypertrophied, inflamed, dark red, ulcerated and covered in spots with grayish areas of necrotic tissue, and Class II—diabetes present, but relatively controlled. Here teeth were firm, mucous membranes soft, flabby, and spongy but no ulcerations. There was extensive loss of alveolar bone and deep pockets with little or no pus. Of fifty-five patients studied only one did not have "periodontoclasia."

During the twenties and thirties, one may find other reports of this nature (Niles (3), Aiguier (4)).

However, other workers were beginning to report differing observations. Thus Ersner in 1926, concluded that diabetes need not necessarily be associated with or accompanied by stomatitis and gingivitis (5). Badanes in 1932, reached a similar conclusion (6).

Lovestedt and Austin in 1943, in a study of 503 diabetics and 1023 controls (7) concluded, "clinical findings in Diabetic cases failed to differ essentially from the findings in the control cases. In fact, patients with long standing and controlled diabetes are invariably free from dental infection; this, if it ever existed, having been eliminated previously in an effort to be rid of all potential foci of infection." Parma, in 1947, after a survey of 306 diabetics considered inflammatory changes to be secondary and neither essential for nor characteristic of changes occurring in diabetes (8).

The study by Ziskin and his associates of histological sections of oral tissues from diabetics (9) revealed changes in insulin treated diabetics which may help to explain some of these later findings. They found hyperkeratinization of epithelium, hyperplasia of connective tissue elements of the corium, and an increase in prominence of the capillary bed. It was suggested that these changes might be influential in combatting gingival infection and thereby explain the lessened incidence of infection. They also found a complete absence of, or decrease in, the cellular inflammatory exudate, even in the presence of long standing infection. The above changes were attributed to insulin.

The changing nature of oral tissue reactions in diabetics therefore becomes evident. The full effect of the introduction of protamine zinc insulin cannot be evaluated as yet.

In our study we have seen nothing in the mouth of the treated diabetic that does not occur in the non-diabetic. The question of relative frequency of occurrence is one we cannot answer. Similar surveys are planned for non-diabetics drawn from the same socio-economic population groups.

Of interest to us were certain reports of nutritional surveys, aspects of which lend themselves to comparison with our findings in spite of differences in age, geography, and socio-economic background. Such a comparison has been effected in table V for those portions of the surveys listed which were comparable with similar portions of our own.

TABLE V

*A Comparison of the Incidence of Certain Tissue Changes in Diabetics and Non-Diabetics*

CHANGES	M.S.H.	NEWFOUND- LAND	SPIES	U.S.P.H.S.
	%	%	%	%
Tongue				
Atrophy of papillae.....	20	32	15	5
Hypertrophy papillae.....	94	35	9	1.8
Fissuring.....	32	7	1	8.8
Lips				
Cheilosis.....	20	68	43	
Gums				
Swelling.....	38	45		
Recession.....	28	52		
Pus.....	9	12		

Spies studied 914 individuals admitted because of nutritional failure to the Hillman Hospital (10). The Newfoundland Survey was carried out amongst the general population of Newfoundland in 1944 and 868 individuals were studied (11). The U.S.P.H.S. Survey was carried out in 1947, and 820 individuals in Alachua County, Florida were studied (12).

As an added instance of the incidence of such changes in non-diabetics, it might be well to cite the work of Metcalf and McQueeny (13) who found an incidence of nonspecific glossitis—82 per cent; non specific gingivitis—44 per cent; non specific cheilosis—9 per cent amongst 386 pregnant or lactating women in the general population of post war Italy.

As was mentioned previously, mechanical factors may play an important role in the etiology of certain of the changes attributed to nutritional and metabolic disturbances.

The association between poorly fitting dentures, loss of vertical dimension and angular lesions of the lips and mouth has been noted.

Ellenberg and Pollack (14) first demonstrated that certain treatment resistant ariboflavinoses (pseudo-ariboflavinosis) were due to poorly fitted dentures and loss of vertical dimension. Their analysis and that of Mann and co-workers (15) clearly delineates the problem. In our present study we have found such an association in about  $\frac{1}{3}$  of the full denture wearers. An equal percentage exhibited some degree of atrophy (flattening) of the papillar of the tongue for which the dentures may have been partially responsible. It should be emphasized that poorly fitting dentures and loss of vertical dimension not only create mechanical

TABLE VI  
*Tooth Mortality*

	NUMBER	PER CENT
1. Incidence of edentulous arches		
upper . . . . .	94	63
lower . . . . .	78	52
2. Number of arches with loss of more than 5 teeth but not edentulous		
upper . . . . .	28	19
lower . . . . .	43	29
3. Reasons for extractions in 1 and 2 above		
periodontal disease . . . . .	56	38
caries . . . . .	27	18
4. Age at extraction		
no definite period . . . . .	42	
Below 30 yrs. . . . .	2	
Between 31-40 . . . . .	10	
Between 41-50 . . . . .	40	
Between 51-60 . . . . .	24	
Between 61-70 . . . . .	3	
5. Irritation beneath dentures		
upper (94 arches) . . . . .		
lower (78 arches) . . . . .		

features leading to the genesis of such lesions, but may contribute to the establishment and maintenance of hypovitaminoses in individuals who cannot masticate efficiently, and in whom gastro-intestinal dysfunction may result.

The influence of traumatic occlusion and calculus formation on gingival changes are also in need of elucidation.

**TOOTH MORTALITY.** The problem of tooth loss in diabetics is a vexing one, especially so since efficient mastication is necessary for optimum digestion and absorption of foods. There are many reports in the literature which imply that the incidence and rate of tooth loss in diabetics is greater than in non-diabetics. However, this opinion is by no means unanimous. We know of no definitive

statistical studies. Our own is not and therefore we cannot go into the question as it merits.

There is no doubt, however, that when failure of tooth retaining structures occurs in certain diabetics, it does so with a precocity and rapidity of progress that are remarkable (aside from any question of specificity). This is especially true in some young individuals. An illustration of one such case is given in fig. 1 showing the roentgenographic appearance of the alveolar bone and teeth in a twenty-two year old diabetic girl. The most striking roentgenographic change is



FIG. 1. Roentgenograms illustrating severe alveolar bone involvement in a twenty-two year old diabetic girl. This condition is also seen in non diabetics.

in the alveolar bone, the density of which is extremely lessened. The nature and cause of this change is not known. The studies of Glickman on alveolar bone changes in alloxan induced diabetic rats (16) are suggestive in that in individual cases a tendency towards a non-specific "osteoporosis" totally unrelated to gingival changes was found.

Intensive study of such cases should contribute much to our knowledge of general bone physiology and pathology.

**NATURE AND INCIDENCE OF ROENTGENOGRAPHIC CHANGES.** Full series intra-oral roentgenograms were obtained in 120 cases. There were 13 persons with retained roots, 3 with impactions and 7 with apical radiolucencies.



The following was found in those individuals who were sufficiently dentulous to permit an appraisal of alveolar bone in terms of resorptive processes, as indicated by increased radiolucency of trabeculae, laminae durae, and cortical bone, and disorganization of any of these structures.

<i>Degree of Resorption</i>	<i>Number of patients</i>
0	6
1	5
2	8
3	19
4	20

Amongst the 48 dentulous individuals there were 13 in whom the amount of bone loss appeared to be greater than clinical examination of the mouth might lead one to expect. In 6 of these patients this discrepancy was very marked. Thus, in approximately one third of these individuals, the clinical appearance of the mouth was not a good index of the roentgenographic appearance of the alveolar bone. In other words inflammatory changes, pocket formation, and gingival pathology are not necessary for bone loss to occur.

This may be contrary to certain empirical teachings accepted as fact by virtue of constant repetition. But it is an observation supported by a wealth of clinical experience. Resorptive and even destructive phenomena often occur in alveolar bone without signs thereof in overlying gingivae. Cysts, granulomas, cementomas, neoplasms, osteidites, fibrous dysplasias, may occur in bone without affecting overlying tissues. Such pathology may be undetected at clinical examination because soft tissues appear to be normal, and not until roentgenograms are taken is the bone pathology revealed.

It should also be noted that the roentgenographic appearance of the alveolar bone varied greatly in different individuals, and at times, in different areas in the same individual. That such variations may be based upon metabolic phenomena has been pointed out by Cahn (17), Becks (18), Glickman (19), and Kronfeld (20).

In an effort to determine whether or not roentgenographic changes were present in other bones of the skeleton, 10 individuals with severe alveolar bone changes were selected for preliminary study. Roentgenograms of the right hand and both femora were obtained. The only changes noted were of an osteoarthritic nature, and varied from mild to severe. This study will be extended in the future.

VITAMIN A AND CAROTENE LEVELS. Early in this study we noted that certain individuals had varying degrees of a yellowish coloration of the soft tissues of the mouth. The palate, floor of the mouth, and lip mucosa were most frequently affected. In the absence of other signs of jaundice it was thought that a carotenemia might be responsible. We therefore, selected 14 such individuals for the estimation of fasting Vitamin A and Carotene blood levels (21). A number of cases of hyperkeratinization of the gingivae and buccal mucosa, Fordyce's granules, and one case of probable leukoplakia were also chosen because they present epithelial changes which may be associated with disturbances in Vitamin

A metabolism. Twenty-one individuals with no oral changes of the above type were selected for control determinations. The results are given in table VII.

TABLE VII  
*Serum Vitamin A and Carotene Levels in Diabetics*

TISSUE CHANGE GROUP				CONTROL GROUP		
Age	Condition present	Vit A	Carotene	Age	Vit A	Carotene
		<i>u</i> %	<i>u</i> %		<i>u</i> %	<i>u</i> %
42	Y	66	295	15	41	178
49	F	57	192	34	46	93
49	FI	75	118	34	56	180
50	YF	96	224	35	50	196
50	F	89	390	37	64	146
51	Y	68	179	42	62	183
55	F	107	139	46	96	110
56	FI	79	110	47	48	123
57	FY	84	207	50	37	193
57	F	63	202	52	42	290
58	F	82	166	52	49	111
59	Y	45	274	53	39	199
60	Y	73	260	54	21	195
60	FY	33	63	58	79	68
60	Y	62	440	58	63	272
61	Y	65	240	61	35	160
63	LY	66	170	62	83	125
66	Y	42	274	65	62	135
67	F	87	321	66	80	112
67	FY	45	175	68	120	171
70	Y	73	269	68	80	112
74	Y	50	111			

Y—Yellowish Coloration

F—Fordyees' Granules

FI—Hyperkeratinization

L—Leukoplakia (probable).

The above data suggest no abnormality in fasting Vitamin A or Carotene levels. The differences between the two groups are not significant statistically and nearly all values fall within the usual ranges obtained with this method.

#### SUMMARY AND CONCLUSIONS

1) A survey of the oral cavity in 149 treated diabetics is reported. Subjective symptoms, and tissue changes found do not differ from those found in non-diabetics. The relative frequency of occurrence of certain changes in diabetics and non-diabetics was compared, using data derived from the literature.

2) The incidence of acute inflammation and infection including pus and polyp formation was low.

3) The role of mechanical factors in the production of certain oral tissue changes was discussed.

4) In many instances the clinical appearance of the gingivae was not found to be an accurate guide to the roentgenographic appearance of underlying alveolar bone.

5) Preliminary skeletal roentgenographic studies in 10 selected cases who exhibited severe alveolar bone loss revealed usual osteoarthritic changes. No osteoporotic changes were noted.

6) No abnormalities in fasting Vitamin A and Carotene levels were found in a group of patients exhibiting yellowish coloration of the soft tissues of the mouth, hyperkeratinization, Fordyce's Granules and Leukoplakia.

7) The role of insulin as a modifier of oral pathology is discussed.

*Acknowledgement.* We wish to thank Dr. Stanley Kollen for his valuable assistance with the roentgenographic phases of this study.

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## ABSTRACTS

### AUTHORS' ABSTRACTS OF PAPERS PUBLISHED ELSEWHERE BY MEMBERS OF THE MOUNT SINAI HOSPITAL STAFF

Members of the hospital staff and the out patient department of the Mount Sinai Hospital are invited to submit for publication in this column brief abstracts of their articles appearing in other journals.

*Progress in the Surgical Treatment of Carcinoma of the Esophagus and Upper Stomach.* J. H. GARLOCK. Surgery, 23: 906, June, 1948.

In this article appearing in a symposium of this issue of Surgery on the Treatment of Cancer of the Esophagus and Upper Stomach, the author describes the progress in the surgical therapy of these diseases during the past 10 years, and emphasizes first the importance of early diagnosis, second the necessity for a microscopic diagnosis obtained through a biopsy specimen, and third the pathological sequence of the disease with respect to lymph nodes and other metastases. He also stresses the importance of considering the surgical treatment of this disease as a group cooperative problem including the combined efforts of the roentgenologist, esophagoscopist, internist, anesthetist, surgeon, operating-room staff, and adequate postoperative nursing care. There is a great deal of stress laid on the importance of preoperative preparation including the appraisal of the patient from all standpoints. The question of anesthesia is gone into rather carefully and also the operative description of the various procedures depending upon the location of the tumor. Finally, the author suggests a method of reporting cases by surgeons all over the world so that there will be a more generalized conformity for statistical purposes. The progress in this field of surgery has been rapid and there has been noticed a rapidly decreasing operative mortality and an increasing number of long term survivors.

*Evaluation of Anginal Pain in Various Stages of Coronary Artery Disease. Particularly the Premonitory Phase of Coronary Occlusion and Infarction without Occlusion.* H. L. JAFFE, H. HALPRIN AND L. M. NELSON. New York State J. Med. 47: 1383, June, 1947.

Acute coronary episodes with angina may be divided into (1) coronary occlusion with through and through infarction, and (2) coronary insufficiency. Coronary insufficiency is of various degrees ranging from the brief classical attack of angina pectoris, which is functional, to more severe ischemia which may produce electrocardiographic changes for several days or lead to subendocardial or progressive necrosis and electrocardiographic changes for several weeks or longer. The type, duration and severity of pain may be similar in coronary insufficiency and occlusion but they can be differentiated by the electrocardiogram in the majority of cases. In insufficiency RS-T depression usually appears whereas in occlusion RS-T elevation and Q-waves are present. A persistent anginal syndrome, beginning abruptly or showing sudden acceleration, may signify infarction without occlusion or the premonitory phase of occlusion. During this phase the electrocardiogram may present the changes of infarction without occlusion. When the occlusion becomes complete, the electrocardiogram assumes a typical pattern. It is suggested that anticoagulant therapy in the stage of impending occlusion may prevent the latter.

*Vitamin E in Heart Disease.* H. LEVY AND E. P. BOAS. Ann. Int. Med., 28: 6, June, 1948.

Vitamin E in very large doses was administered to 13 patients who were examined carefully at regular intervals to determine whether any subjective or objective changes fol-



lowed the use of this substance. Aside from symptoms of headache, dizziness, and vertigo on the higher dosages, there was remarkably little change or effect from this drug, in the following groups: five cases of chronic heart failure; five cases of chronic angina pectoris with a stable pattern of chest pain on effort and finally, three cases of angina pectoris in states of coronary insufficiency with increased frequency and intensity of anginal attacks.

*Vitamin E in Heart Disease.* HYMAN LEVY. *Ann. Int. Med.*, 28: 1117, June, 1948.

In the attempt to corroborate clinical improvement noted by others in the treatment of various forms of heart disease with vitamin E, a carefully selected and controlled group of patients were followed periodically, while vitamin E was administered in daily doses ranging from 200-800 mgms. Three distinct categories of heart diseases were used, namely, (1) chronic angina pectoris with a stable pattern of pain, (2) active coronary symptoms characterized by frequent anginal attacks often at rest and, (3) chronic heart failure on the basis of long standing rheumatic cardiovalvular disease. In none of the 13 patients studied was there any subjective or objective evidence of improvement. This clinical study found no evidence to substantiate the claims that  $\alpha$ -tocopherol benefits these forms of heart disease.

*Digitoxin Intoxication.* A. M. MASTER. *J.A.M.A.*, 137: 531, June, 1948.

Digitoxin has practically replaced digitalis U. S. P. (digitalis leaf), but the dangerous aspects of its administration have been disregarded and digitoxin intoxication has become frequent. Clinical observations confirm the pharmacologic fact that digitoxin has the greatest cumulative action (slowest dissipation) of all the glycosides. The dosage of 1.2 mg. as a single digitalizing dose and of 0.2 mg. for maintenance has often been applied indiscriminately to patients regardless of weight, without proper surveillance of the patient and without awareness of the dangers involved in using the drug. It must be remembered that the daily maintenance dose of digitoxin varies from 0.05 to 0.2 mg.

*The Association of Psychosomatic Disorders and Their Relation to Personality Types in the Same Individuals.* E. MOSCHOWITZ AND M. B. RONDIN. *New York State J. Med.*, 48: 1375, June, 1948.

A study was made to note the frequency of association of psychosomatic disorders in the same individual. The following psychosomatic disorders were selected: essential hypertension, Graves' syndrome, peptic ulcer, colonic disorders, including mucous "colitis", spastic "colitis" and nonspecific ulcerative colitis, and cardiospasm. We submitted the thesis that in the production of psychosomatic disorders the following biologic sequence may be constructed: Constitution times psychologic trauma gives hyperkinesis which results in psychosomatic disease. We believe that the variety of psychosomatic disease which will be engendered is related to the type personality and not to the specific kind of psychologic trauma. The type personality coincident with these various psychomatic diseases is described. In the description of these types a considerable overlapping is noted, accounting for the association of certain psychosomatic disorders in the same individual. This accounts for the not infrequent association of hypertension and peptic ulcer, and Graves' syndrome and colonic disorders. On the other hand, the invariable precedence of one psychosomatic disorder to the other is a strong indication that the first disorder acts as an activating agent. This applies to the sequential relation of essential hypertension to Graves' syndrome, of peptic ulcer to Graves' syndrome, and of cardiospasm to peptic ulcer. No instance of the association of peptic ulcer and nonspecific ulcerative colitis was noted in our series, and we believe this is due to the fact that the personalities of the two diseases are antithetic.

*Differential Diagnosis of Diaphragmatic Hernia and Coronary Heart Disease.* S. DACK, J. STONE, A. GREISHMAN, AND A. M. MASTER. *Bull. N. Y. Acad. Med.*, 6: 396, June, 1948.

This report is based on a study of 50 consecutive patients with diaphragmatic hernia.

About one-fourth had gastrointestinal complaints alone. A few presented only cardiovascular symptoms. Almost three-fourths of the patients had a combination of dyspepsia, dysphagia, and the like, and such symptoms as pain in the chest, palpitation of the heart, and rapid heart rate. To determine the existence of organic coronary disease, the following clinical examinations were done: teleoroentgenogram, roentgenoscopy, resting electrocardiograms, including Wilson unipolar precordial and extremity leads, the "2-step" exercise electrocardiograms and the 10 per cent anoxemia test. The authors arrived at the conclusion that uncomplicated diaphragmatic hernia gives no objective evidence of coronary artery disease. When chest pain is present, it is usually not associated with effort. With rare exceptions, when precordial or substernal pain on effort occurs in the presence of diaphragmatic hernia, the foregoing objective tests uncover the customary evidence of organic disease of the coronary artery.

*Cancer of the Lung. Interval and Late Results of Operation in Relation to Topography and Gross Pathology.* HAROLD NEUHOF AND ARTHUR H. AUFSES. *J. Thorac. Surg.*, 17: 297, June, 1948.

Interval and late results are reported on 52 patients who survived operation. They have been classified in 3 groups. The operations performed in each were: Group I, 20 pneumonectomies and one lobectomy; Group II, 12 lobectomies and 6 pneumonectomies; Group III, 12 lobectomies and 1 pneumonectomy. In Group I (the main bronchus cancer) there were no survivals in patients with extensive regional node involvement in the specimen. Involvement was limited, or absent, in the 7 patients who survived. An unexpectedly high occurrence of blood-borne metastases was the fatal factor, especially in the cases without lymph node involvement at the time of operation. In Group II (circumscribed cancer) lymph node involvement at the time of operation was rare, yet lymph node metastases as the cause of death was unexpectedly high. The incidence of blood-borne metastases was surprisingly low. Lobectomy is not curative in the presence of lymph node involvement. Despite the absence of regional node involvement, the results were poor in Group III (peripherally invasive cancer) due to local recurrence, usually in the thoracic parietes. Results might be better with wider excision of the thoracic wall. The microscopic features of cancer of the lung bear no significant relation to the ultimate postoperative prognosis. The prognosis after a correctly selected operation for circumscribed cancer of the lung is better than that for main bronchus cancers. Lobectomy is a properly conceived operation which may be curative for circumscribed and peripherally invasive carcinoma of the lung. A substantial proportion of good interval and late results has been achieved by pneumonectomy or more conservative operations performed on the basis of the topographic features of the neoplasm. There is full justification for an enthusiasm for the surgery of cancer of the lung when eradication is based upon the recognition and consideration of the topographic features.

*Phosphorus Poisoning with Recovery Accompanied by Electrocardiographic Changes.* R. A. NEWBURGER AND S. B. BEASER. *Am. J. Med.*, 4: 927, June, 1948.

A case of phosphorus poisoning in a 21 year old Puerto Rican soldier is reported. As much as 1.5 gm. of white phosphorus may have been ingested. Within two to three hours the patient was lavaged with 3% hydrogen peroxide and 1% copper sulfate. Patient was never critically ill. The significant laboratory findings were (1) a transient decrease in the total white cells and polymorphonuclear leukocytes, (2) depression of liver function lasting two to three months and (3) change in the electrocardiogram of six weeks duration consisting of lowering of voltage of T1, 2 and 4, isoelectric T3 and straightening of the ascending limb of T1 and 2. In addition there was coveplaning of T4. The T wave changes were suggestive of changes previously reported in cases of toxicity due to Faudin and other cardiotoxins.

*Electric Shock Treatment in Advanced Pregnancy.* L. SIMON. *J. Nerv. & Ment. Dis.*, 107: 579, June, 1948.

Three cases of electric shock treatment during pregnancy are reported. In 2 of these, the last electroconvulsion was within a month of delivery, with good results psychiatrically and obstetrically. In the remaining case, the shock treatments were given during the middle trimester, with psychiatric improvement, but the patient reported to a later inquiry that she had had a toxic pregnancy and that the baby died 2 days after birth at term.

*Treatment of Multiple Myeloma with "Stilbamidine". Clinical Results and Morphologic Changes.* I. SNAPPER. J.A.M.A., 137: 513, June, 1948.

In 80% of the cases of multiple myeloma the pains are at least partly relieved by intravenous or intramuscular injections of "stilbamidine" (4,4'-stilbenedicarboxamidine). The disease is at best halted temporarily; relapses are frequent, and Bence-Jones proteinuria and increase of globulin in the serum are not influenced. The drug should be handled with care in patients who have impaired renal function, as is frequently the case in Bence-Jones proteinuria. The drug has no deleterious influence either on hepatic function or on the peripheral blood picture. In the majority of the cases a dissociated anesthesia of the trigeminal branches sets in several months after the termination of treatment. This anesthesia does not lead to dangerous complications, although occasionally disagreeable subjective complaints of itching of the eyes have occurred. After treatment with "stilbamidine," a specific alteration of the cytoplasm of the myeloma cells is observed, consisting of the formation of precipitates of ribonucleic acid conjugated with "stilbamidine." It is probable that the nucleoproteins of the cytoplasm of the myeloma cells are different from the nucleoproteins of any other cells in the body. "Stilbamidine" evidently has a specific affinity for these abnormal nucleoproteins of the myeloma cells.

*Medical Aspects of an Alcoholic Service in a General Hospital. Preliminary Report.* M. TEXON. New York Med., 4: 22, June, 1948.

The alcoholic is emphasized as a sick person who is primarily a medical problem. The origin, cooperation with Alcoholics Anonymous, and plan of the Alcoholic Pavilion of Knickerbocker Hospital are briefly described. The age, sex incidence, and medical conditions encountered in 200 consecutive alcoholics are tabulated. Criteria for the clinical classification of hepatic disease found in alcoholics are given. Fatty liver is the most common clinical diagnosis and appears directly proportional to the duration of alcoholism. The need for further work in this important field is outlined.

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## CONTENTS

	PAGE
HYALURONIDASE INHIBITOR OF HUMAN BLOOD SERUM IN HEALTH AND DISEASE. <i>David Glick, Ph.D.</i> .....	207
BACTERIOLOGICAL ASPECTS OF THE PATHOGENESIS OF TUBERCULOSIS. <i>Rene J. Dubos, Ph.D.</i> .....	229
THE EFFECTS OF THE SINGLE AND DOUBLE "TWO-STEP" EXERCISE TESTS UPON THE ELECTROCARDIOGRAMS OF 200 NORMAL PERSONS. <i>Leonard Scherlis, M.D., Avery A. Sandberg, M.D., Joseph Wener, M.D., Joseph Drorkin, M.D., and Arthur M. Master, M.D.</i> .....	242
AMYLOID DISEASE OF THE URINARY BLADDER. <i>H. E. Leiter, M.D.</i> ...	254
CARCINOID OF THE DUODENUM. <i>Charles Polivy, M.D.</i> .....	260
OBITUARY—DR. MEYER .....	265
ABSTRACTS .....	267
BOOK REVIEW .....	268



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## HYALURONIDASE INHIBITOR OF HUMAN BLOOD SERUM IN HEALTH AND DISEASE\*

DAVID GLICK, Ph.D.†

Life seems to be maintained in a range between opposing forces operating simultaneously, and life processes can continue so long as the systems of checks and balances, inhibitions and activations of the basic chemical reactions are maintained within this range of physiological equilibria. It is a fundamental law of the inanimate, as well as of the living realm, that when a stress is applied to any dynamic system, the system will react to relieve this stress by an appropriate shift in the balance of the opposing tendencies. The freshman chemistry student learns of this law as Le Chatlier's principle, the biologist and physician learn of it as physiological homeostasis. But not only does this law apply to the changes within an organism, but also to the relationships between organisms. Throughout a wide range in the evolutionary scale we can observe a balance between the special offensive properties with which the predator is endowed and the matching defenses of the prey. The partial success of each prevents either from becoming extinct.

A particularly intriguing predatory agent utilized by many organisms, from bacteria to some of the higher animals, in their attack on prey is hyaluronidase. Thus the Welsh bacillus that permeates tissues with such lethal effect, the streptococcus that erodes the lining of the heart valves, the larva of the *Schistosoma mansoni* that bores through the skin, the venoms of the bee and snake that spread through the tissues of their victims, and the spermatozoon that penetrates the ovum—all utilize hyaluronidase to abet their respective purposes. The mucoid substances that glue the cells together or coat the ova also serve normally as barriers to the spread or penetration of foreign bodies or materials. As a constituent of many of these mucoids, the polysaccharide, hyaluronic acid, appears to be a key object of the many invasive agents that contain the enzyme which specifically hydrolyzes and liquifies this viscous intercellular mortar.

In line with the previous remarks, it is not of the order of things in nature that an attacking force can proceed unchecked even when the attacker, as in the present case, is specifically designed to assault and demolish an important protective structure. The higher forms of life possess at least two mechanisms that can deal with the hyaluronidase of the invader, and therefore tend to maintain the integrity of the defensive intercellular walls. One of these is the mobilization of antibodies to inactivate the hyaluronidase. The antibodies

\* A lecture in the series on Recent Advances in Disorders of Metabolism, given at The Blumenthal Auditorium, The Mount Sinai Hospital, New York, March 22, 1950. The author's investigations were aided by grants from the Division of Research Grants and Fellowships, National Institute of Health, U. S. Public Health Service, Bethesda, Md., and the Medical Research Fund of the Graduate School, University of Minnesota.

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elicited by the foreign protein of the enzyme can inhibit the action of the enzyme, but of course this inhibition is specific in the immunological sense, so that the antibody developed against the enzyme from one species cannot inhibit the same enzyme from another. But aside from this specific defense to a given source of hyaluronidase, a defense, unfortunately, that is not immediately available and involves a time factor that can render it useless in some cases, all higher animals have been shown to possess another, far more general, protector against the enzyme. The latter factor is always present in the blood serum, it is immediately available if the need arises, and it can inhibit the activity of hyaluronidase from any source. It is this ever-present, generally-applicable defensive factor that is the subject of the present discussion.

A viscosimetric method was employed to determine the hyaluronidase activity and its inhibition. Hyaluronic acid prepared from human umbilical cords was used for the substrate, and the hyaluronidase was obtained from bull testes. A measure of the viscosity of the reaction mixture was obtained by determining its

TABLE 1  
*Hyaluronidase Inhibitor in Human Plasma*

	NORMAL	POLIOMYELITIS IN ADULTS
No. Observations	30	27
Mean Concentration A/ml. serum $\pm$ Std. Error of Mean	12.4 $\pm$ 1.1	24.6 $\pm$ 2.1
Difference of Means $\pm$ Std. Error of Difference of Means	12.2 $\pm$ 2.4	
t. ....	5.14	
P ....	<0.001	

outflow time in a viscosity U-tube. The time required for the enzyme to reduce the viscosity to half its initial value was measured in both the presence and absence of serum. The difference in the "half-times", due to the enzyme inhibition by the serum, divided by the "half-time" of the uninhibited reaction, represents the unit of inhibitor, called an A unit, which was employed in our early work, after the convention of Haas (1). Subsequently, inhibitor values were expressed in terms of per cent inhibition and the empirical A unit was discarded (2).

#### INFECTIOUS DISEASES

The first phase of our studies on the non-antibody inhibitor of hyaluronidase dealt with infectious disease processes. At the time, Minnesota was experiencing a bad outbreak of poliomyelitis so we directed our initial efforts to the observation of the influence of the course of this disease on the blood level of the inhibitor (3). With Dr. Frank Gollan of the Physiology Department, samples of blood plasma from 27 active cases in the age group 18-35 years were compared with those from 30 normal individuals in this age group. The data, statistically treated, are shown in Table 1. It is apparent that a significant elevation above

the normal was found in the polio patients. Follow-up studies on 9 of the patients revealed that the magnitude of the inhibitor value was proportional to the severity of the disease. The value fell to normal during recovery. In the terminal

TABLE 2  
*Summary of Data on Skin Diseases*

DISEASE	NO. CASES	MEAN A/ML.
Normals.....	121	11
Pemphigus vulgaris.....	9	72
Lupus erythematosus, acute.....	1	137
Lupus erythematosus, subacute.....	3	25
Lupus erythematosus, chronic.....	4	13
Lupus vulgaris.....	1	104
Syphilis primary.....	1	34
Syphilis secondary.....	3	10
Syphilis tertiary.....	4	22
Syphilis tertiary (malaria therap.).....	5	66
Erythema induratum.....	2	19
Erythema multiforme.....	3	27
Erythema nodosum.....	2	67
Chicken pox.....	1	42
Kaposi's varicelliform eruption.....	1	43
Herpes zoster.....	3	31
Dermatitis herpetiformis.....	2	22
Molluscum contagiosum.....	1	5
Verruca vulgaris.....	3	5
Psoriasis vulgaris.....	8	30
Erysipelas.....	2	60
Cellulitis.....	1	34
Impetigo.....	1	81
Pyoderma gangrenosum.....	2	35
Kerion.....	2	22
Blastomycosis.....	1	26
Mycosis fungoides.....	2	36
Lymphoblastoma.....	1	22
Sarcoidosis.....	2	25
Dermatomyositis, chronic.....	2	18
Benign familial pemphigus.....	2	9
Lichen planus.....	2	15
Pityriasis rubra pilaris.....	1	25
Epidermolysis bullosa.....	1	18
Xeroderma pigmentosum.....	2	11

stages of fatal cases the inhibitor level declined, but at death the values were still abnormally high.

In order to establish this result further, similar data were collected on 3 monkeys and 128 mice which had been experimentally infected with poliomyelitis, and the results were in accord with the findings in the humans.

The question then arose as to how specific this effect might be. With the



collaboration of Dr. Melvin Grais of the Division of Dermatology, a survey investigation of the serum inhibitor in a wide variety of both bacterial and virus diseases was undertaken. The first study (4) was devoted to skin diseases, and included some of unknown etiology in addition to the bacterial and virus varieties. Whenever possible, serum analyses were carried out on the patient during the entire course of his disease. Otherwise, single samples of sera, taken at the height of the disease, were used. An attempt was made to correlate the inhibitor levels with the clinical condition, temperature, erythrocyte sedimentation rate, and total leucocyte count. To summarize this work the data in Table 2 are given.

TABLE 3

*Concentrations of Drugs Having No Effect on Hyaluronidase or the Serum Inhibitor*

DRUG TESTED	THERAPEUTIC CONCENTRATION	HIGHEST CONCENTRATION TESTED OF DRUG IN SERUM WITH NO EFFECT ON INHIBITOR	HIGHEST CONCENTRATION TESTED OF DRUG IN HYALURONIDASE SOLUTION WITH NO EFFECT ON ENZYME ACTIVITY
Penicillin .....	30 U/ml. serum	500 U/ml.	100 U/ml.
Streptomycin .....	20 U-60 U/ml. blood	250 U/ml.	100 U/ml.
Sulfanilamide .....	10 mgm.% in blood	20 mgm.%	50 mgm.%
Sulfapyridine .....	4-6 mgm.% in blood	50 mgm.%	20 mgm.%
Pyribenzamine .....		50 mgm.%	10 mgm.%
Mapharsen (30% arsenic) .....	0.1 mgm.% As in blood	30 mgm.% As	0.6 mgm.% As
Gold sodium thiosulfate (37% gold) .....		3.7 mgm.% Au	0.74 mgm.% Au
Thiobismol (38% bismuth) .....	0.0057 mg.% Bi in blood	19 mgm.% Bi	3.8 mgm.% Bi

Since many of these patients were receiving chemotherapy at the time the sera were taken for analysis, it was necessary to determine whether the drugs involved could influence the measurements. Accordingly, the data presented in Table 3 were obtained from *in vitro* experiments, and it may be seen that within, and exceeding, the therapeutic range by a wide margin, no effect by any of these drugs on either hyaluronidase or the inhibitor was observed. We are probably safe in assuming then that the data in Table 2 were not directly influenced by the compounds administered.

As previously stated, serial studies were made on each patient throughout the course of his disease when this was possible. An example is given in Chart I. Syphilis itself has little affect on the inhibitor level, but when malaria therapy is instituted, as it was in this case after the 4th day, the inhibitor, temperature, and sedimentation rate all rise. After treatment has been discontinued (25th day), the inhibitor value recedes toward the normal and, of course, so does the temperature and sedimentation rate. An artificial fever, induced by hypertherm

cabinet therapy, has no significant effect on the inhibitor as seen in Chart II. The hematocrit measurements were included to indicate possible hemoconcentration during the treatment, but apparently this did not occur.

From the data on skin diseases several conclusions could be drawn. First, the elevation of the hyaluronidase inhibitor in blood serum was non-specific, though significant, in a wide variety of skin diseases regardless of whether the disease was of bacterial, viral, or unknown etiology. An essential requirement for the elevation was acute systemic involvement; the values were in the normal range when the lesion was localized, and no systemic change was apparent. Then it appeared that when elevated values were found, a correlation existed between the degree of this elevation and the extent of the clinical involvement. Relative

CHART I

*Mr. H. H. Age 40. C.N.S. Syphilis—malaria therapy*

	DAY AFTER ADMISSION									
	2	4	9	11	14	16	18	21	23	25
A per ml.....		13		89		67		55		37
Temp.—high.....	98.0	98.6	102.4	103.6	102.0	105.4	103.5	103.0	106.0	99.4
Sed. rate—mm. in 60 min.....	6		16	116	95	60	40		63	
WBC.—total.....								5800		

CHART II

*Mr. J. B. Age 42. C.N.S. Syphilis—hypertherm cabinet therapy*

	TIME			
	8:30 a.m.	10:30 a.m.	2:30 p.m.	3:30 p.m.
A per ml.....	29	22	24	27
Temp.—high.....	98.6	105.4	104.8	100.2
Sed. rate—mm. in 60 min.....	69	67	71	
Hematocrit.....	41	41	40	41
WBC.—total.....	6200	4500	6300	5950

concomitant changes in temperature, sedimentation rate, and total leucocyte count will be taken up later. Before leaving this consideration of skin diseases it might be mentioned that the bullous fluid from patients with pemphigus had no hyaluronidase activity, and the inhibitor concentration was somewhat less than that in the blood serum of the same individual. Transudates and exudates not contaminated with micro-organisms in general have this lower inhibitor level with respect to the serum.

This study was then extended to include additional infectious diseases (5) and a summary of the data is given in Table 4.

It may be noted that the mean normal value was 16 instead of 11 or 12 as found previously. This was the result of changes in our assay procedure which were introduced to increase the reliability of the method. Since an adequate

number of normal controls were included in each of these studies, this factor did not disturb the conclusions that could be drawn. These conclusions were essentially the same as those from the study on skin diseases, and the correlation of the inhibitor values with the other data on the same patients may be seen in Table 5. It is obvious that a significant correlation maintains between the inhibitor level and both the sedimentation rate and temperature, but not between the inhibitor level and total leucocyte count. While the inhibitor and sedimentation rate showed parallel changes in most of the systemic infectious diseases

TABLE 4  
*Summary of Data for Certain Additional Diseases*

DISEASE	NUM- BER OF CASES	AGE RANGE	MEAN SEDIMENTA- TION RATE (MM. IN 60 MIN.) AND STANDARD ERROR OF THE MEAN	MEAN A/ML. AND STANDARD ERROR OF THE MEAN
		years		
Subacute bacterial endocarditis.....	6	18-61	104.0 $\pm$ 4.8	44 $\pm$ 5.0
Chronic rheumatoid arthritis.....	17	27-80	60.8 $\pm$ 13.9*	22 $\pm$ 5.1
Brucellosis.....	3	32-52		27 $\pm$ 5.6
Pertussis.....	1	27	35	39
Scarlet fever.....	1	24	11	28
Primary atypical pneumonia.....	3	20-44		48 $\pm$ 16.4
Infectious mononucleosis†.....	14	17-32		19 $\pm$ 3.5
Measles.....	1	29		46
Normals.....	90	16-80		16 $\pm$ 0.6

\* Mean of 5 cases.

† Heterophile titers ranged from 1:56 to 1:896. No correlation with A values noted.

TABLE 5  
*Correlation of the Hyaluronidase Inhibitor Values in Blood Serum with Values of Other Measurements on the Same Patients*

MEASUREMENT	NUMBER OF CASES	COEFFICIENT OF CORRELATION	K	P
Erythrocyte sedimentation rate.....	129	0.4	4.5	<0.001
Temperature.....	414	0.3	6.1	<0.001
Total leucocyte count.....	104	0.1	1.0	0.317

studied, the two are probably not interdependent but rather they are separate manifestations of the disease process. This is illustrated in a disease such as brucellosis in which the sedimentation rate is usually not abnormally elevated although the inhibitor level is.

In the course of this work, we had the opportunity of observing the effect of vaccinia vaccination on the serum inhibitor level of college students. In the group, 12 were primary takes and in these the inhibitor level at least doubled its prevaccination value between the 10th and 13th day after vaccination. This also is the period in which the maximum response to the vaccination occurs. In

cases of accelerated reaction, the maximum response usually occurs before the 10th day, and in 6 out of the 7 in this group the inhibitor elevation occurred before the 10th day. In both groups the magnitude of the elevation paralleled the intensity of the reaction. The 16 individuals with immune reactions showed negligible changes in the inhibitor. Care was taken to be sure that none of these persons had developed colds or other sickness during the period of observation.

When it could be arranged, serum inhibitor studies were carried out on laboratory animals to establish more firmly the conclusions that evolved from this

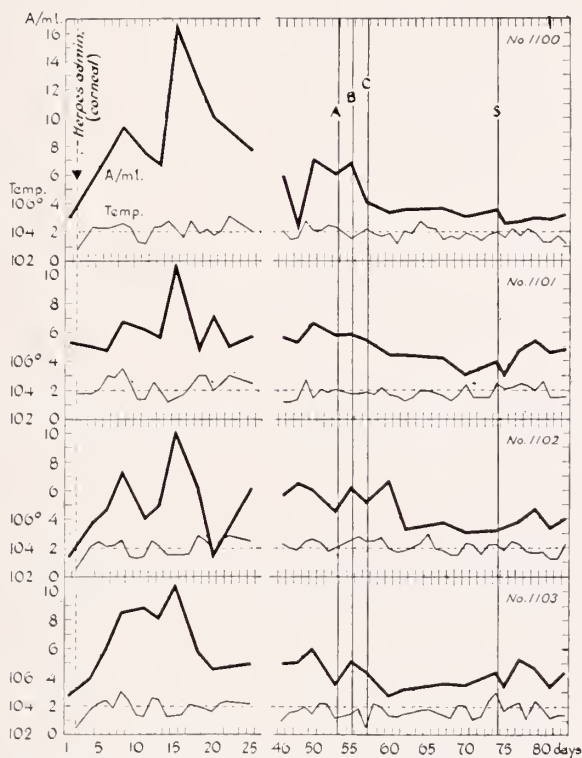


FIG. 1. Effect of herpetic infection via the cornea, and subsequent sensitization to egg white and shock on the level of hyaluronidase inhibitor in rabbit serum. A, B, C represent the time of sensitizing injections and S the time of the shock injection.

work and to yield information not ordinarily available from the studies on humans. One such investigation followed from the work of Good and Campbell (6) who had shown that anaphylactic shock can precipitate an active encephalitis in rabbits in which *Herpes simplex* virus infection is latent after recovery from an attack of the disease. Accordingly, a study of the effect of experimental herpes, and its reinduction by anaphylaxis, was undertaken with the collaboration of Dr. Berry Campbell of the Department of Anatomy (7). From Figure 1 it can be seen that infection in the rabbit via the corneal route results in an elevation of the serum inhibitor which has a characteristic double peak during the period of acute illness. In animals which survive, after infection through the cornea, it



is usually difficult to precipitate a new attack of the disease, or as severe a one, by shock, and from the Figure it is apparent that shock had little effect on the inhibitor level in these animals. On the other hand, when the herpes is induced by leg injection of the virus, it is known that the animals usually do not develop the acute symptoms and high fever characteristic of the corneal route, and in Fig. 2 it may be seen that the serum inhibitor also undergoes less change. However, if shock is applied to rabbits which survive the leg-administered herpes, precipitations of the acute disease often occur. In Figure 2, animals No. 1372 and 1373 which developed the most severe symptoms after shock were the ones showing the pronounced rise in the inhibitor level, while animal No. 1366 evinced

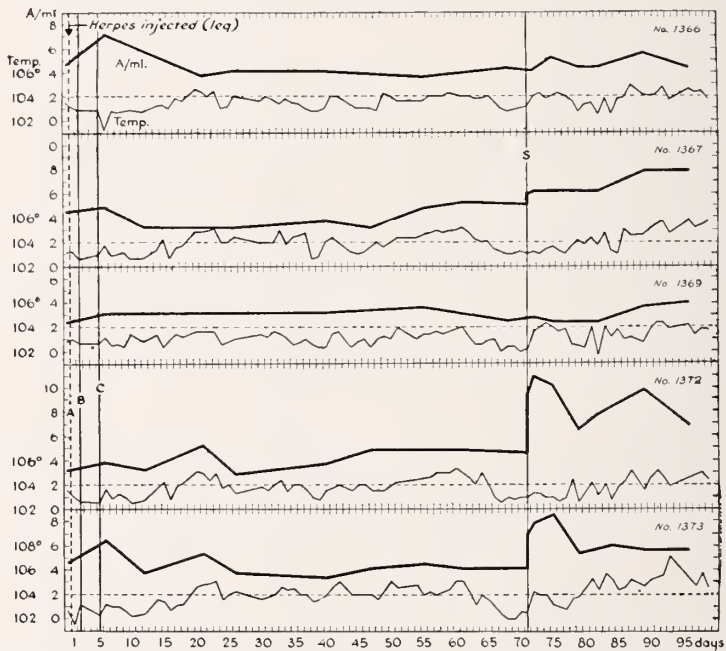


FIG. 2. Effect of herpetic infection via the leg and subsequent anaphylactic shock on the level of hyaluronidase inhibitor in rabbit serum. A, B, C, represent the time of sensitizing injections and S the time of the shock injection.

less of a symptomatic effect and less of an inhibitor elevation. Animal No. 1369 appeared to be unaffected and showed no significant increase in the inhibitor. Control experiments on shock *per se* reflected no consistent change in the inhibitor level.

In these considerations of the inhibitor effects induced by infectious agents, the group of so called "collagen diseases" is of particular interest. A causative relationship can be contemplated between the injury to synovial tissues and connective tissues in general on the one hand, and the hyaluronidase action of organisms that have been implicated in some of these diseases on the other. Lupus erythematosus and dermatomyositis have been considered earlier in this discussion, as was rheumatoid arthritis. Dr. Robert Good, of our Pediatrics

Department, joined us in this endeavor and data in Table 6 on rheumatic disease was collected (8). At this time we had already adopted per cent inhibition as the expression of inhibitor value, and this change will be noted in the table. In previous work, no relation between age or sex and inhibitor level was found in a total of over 200 normal adults. From Table 6 it would appear that the lack of a relationship between these factors can be extended to children as well. This is at variance with the claim of Dorfman *et al.* (9) that males of reproductive age have significantly lower inhibitor values than those of any other group studied.

The data in Table 6 make it clear that a significant elevation of the serum inhibitor occurs in acute exudative rheumatic fever and in acute streptococcal pharyngitis. In these cases a parallelism between sedimentation rate, temperature, and inhibitor was found in accord with the studies on other infectious diseases, and again it was found that the severity of the disease was related to

TABLE 6  
*Hyaluronidase Inhibitor in Normal and Rheumatic Children*

GROUP	NUMBER OF CASES	AGE	MEAN % INHIBITION	S.E. OF MEAN
Normal adults	25	18-48	20.3	$\pm 1.48$
Normal children	8	1- 3	22.1	$\pm 1.53$
	9	4- 6	26.0	$\pm 1.98$
	16	7-11	20.3	$\pm 1.09$
	17	12-18	20.0	$\pm 1.34$
	50	1-18	21.5	$\pm 0.71$
Acute Rheumatic Fever	20	4-22	41.8	$\pm 2.39$
Convalescent Rheumatic Fever	10	4-15	12.9	$\pm 1.13$
Inactive Rheumatic Fever	50	5-20	15.7	$\pm 0.76$
Sydenham's chorea	14	7-14	16.5	$\pm 1.80$
Streptococcus Pharyngitis	10	3-15	31.2	$\pm 4.60$

the degree of the elevation of the inhibitor level. A typical example is illustrated in Figure 3.

The subnormal inhibition values that were associated with convalescent and inactive rheumatic fever offer some grounds for speculation. From extensive clinical studies it has been established that patients in these groups are more susceptible to rheumatic disease than normal individuals. If, indeed, hyaluronidase plays a role in the pathogenesis of rheumatic fever, the lowered inhibitor level might be a factor in enhancing the susceptibility.

The obvious difference between the inhibitor values in acute Sydenham's chorea and acute exudative rheumatic fever is not so surprising when it is recalled that the former rarely shows the changes in sedimentation rate and temperature which are associated with carditis, polyarthritides and subcutaneous nodule formation.

Epstein *et al.* (10) stated that they found no significant relation between the serum inhibition and the clinical state in patients with rheumatic fever. This

statement is in conflict with the findings just presented, but upon inspection of the data used to support the statement, our differences are largely resolved. The data were given as a collection of single values without statistical treatment or even calculation of averages. If one examines these data it is found that an elevation in the inhibitor has actually occurred in the acute rheumatic fever group as compared to the controls. Thus, the mean per cent inhibition with the standard error of the mean for the 15 cases listed as active rheumatic fever without antecedent illness is  $40 \pm 5.7$  as opposed to  $29 \pm 4.0$  for the 28 corresponding normal controls. However, chorea was included as active rheumatic fever, a classification that, for the present purposes, is in some doubt in the opinion of our own pediatricians. If the rheumatic group is considered without the chorea cases, a mean of  $49 \pm 7.0$  is obtained. The difference from the normal

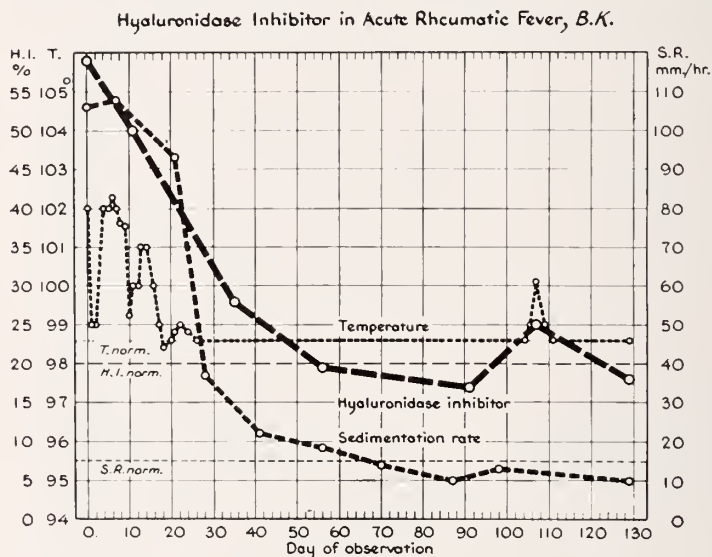


FIG. 3

would, no doubt, be still greater if the assay procedure that was used were improved since the spread of values within each group is abnormally large, and values such as zero per cent inhibition were reported. In our experience with many hundreds of human sera of all types, a zero value has not once been found, and I believe that is also the experience of others.

Before leaving this section on infectious diseases, it is appropriate to call attention to the possibility that the parasites that can infest animal tissues may also employ hyaluronidase for their invasive purposes. Levine *et al.* (11) have already demonstrated that cercariae of *schistosoma mansoni* contain hyaluronidase, and, with the collaboration of Dr. F. G. Wallace of our Zoology Dept., we have underway an investigation of hyaluronidase in other parasites. Dr. R. N. Bieter and his coworkers (12) in our Dept. of Pharmacology found that certain 8-amino quinolines exerted a rather great chemotherapeutic effect in

mice infected with *schistosoma mansoni*, while other chemically related compounds were relatively ineffective. An attempt was made, therefore, to determine whether the difference in the action of these compounds was reflected in their effect, *in vitro*, on hyaluronidase or the serum inhibitor (13). Two substances with the marked chemotherapeutic effect were studied, and both exhibited pronounced inhibition of hyaluronidase. At certain concentrations they also reduced the serum inhibition, but the enzyme activity was completely abolished at higher concentrations whether or not serum was present. On the other hand, two compounds which were therapeutically ineffective had no direct influence on the hyaluronidase activity, although some potentiation of the serum inhibition was observed. The correlation of the effects of the compounds on the enzyme and as therapeutic agents heightens the possibility that the inhibition of the hyaluronidase in the parasite may be connected with the beneficial drug action.

#### CANCER

An intriguing phase of hyaluronidase research is the role of this destructive agent in cancer. It has occurred to many that the malignant cell may utilize hyaluronidase to aid its relentless course of invasion, and, indeed, the literature contains a number of reports of studies on the occurrence of the enzyme in tumor tissue. Unfortunately, however, the reports are inconclusive and often inconsistent. A critical inspection of the work reveals that microbiological sterility of the tumor extracts was not maintained, and, hence, it is not certain whether the enzyme activities reported were due to the tumor tissue or to contaminating organisms. With the collaboration of Drs. L. B. Kiriluk and A. J. Kremen of the Surgery Dept. (14), and Dr. E. Y. Hakanson, a reinvestigation of this problem was undertaken to try to settle, in an unequivocal fashion, whether or not hyaluronidase is actually contained in malignant tissue.

Clean, non-necrotic samples of human tumor tissue were obtained directly from the operating room under sterile conditions. Precautions were taken to maintain sterility throughout the preparation of extracts for enzyme assay, and microbiological controls accompanied various steps in the process. For each tumor examined, separate cultures were made of the fresh tissue, the homogenized tissue, and the final extract. Three culture media were used in each case so that 9 cultures were set up for each sample. When a positive culture was obtained identification of the organism was carried out with routine identification media.

The data in Table 7 show that in 4 different human benign tumor extracts, and in 6 malignant, no hyaluronidase could be detected. The evidence indicates that all of these tissues were sterile when removed from the patient, and that positive cultures which did result were due to subsequent contamination in handling. Thus, the mold found in tumor No. 2 proved to be identical with one used the previous day in the same innoculating hood. For tumors Nos. 6 and 9, only 1 culture was positive out of the 9 in each case, and for No. 11 all samples were positive on 1 medium but not on the other 2. The degree of contamination when it did occur was minimal. In contrast, in a preliminary study (15) on 25 malignant human tumors and as many samples of normal control tissues, all of



TABLE 7  
Decrease in viscosimeter outflow time (seconds) of hyaluronic acid substrate after 18 hours at 38°C\*

TUMOR TYPE	TUMOR EXTRACT	CONTROL	CULTURES		
			Brewer's fluid thioglycollate medium	Todd-Hewitt medium	Lactose or tryptose broth
<i>Benign, human</i>					
1. Lymphangioma of pancreas	0.0	1.5	(-)	(-)	(-)
2. Lipoma	1.0	1.5	Mold in all	Mold in all	Mold in all
3. Lipoma	0.0	0.0	(-)	(-)	(-)
4. Thyroid adenoma	1.0	1.0	(-)	(-)	(-)
<i>Malignant, human</i>					
5. Fibrosarcoma (no metastasis)	1.0	0.5	(-)	(-)	(-)
6. Breast carcinoma (metastasized)	0.5	0.5	(-)	(-)	Only extract (+) (Tryptose) for coag. pos. hemolyt. staph.
7. Mixed tumor of oropharynx (metastasized)	0.0	1.0	(-)	(-)	(-)
8. Lung squam. cell carcinoma (metastasized)	1.0	1.5	(-)	(-)	(-)
9. Carcinomatous mixed tumor of testis (metastasized)	0.0	0.0	(-)	(-)	Only extract (+) (Tryptose) for alpha and beta hemolyt. strep.
10. Carcinomatous mixed tumor of testis (metastasized)	1.0	0.0	(-)	All (+) for alpha and beta hemolyt. strep.	(-)
<i>Malignant, mouse*</i>					
11. Breast adenocarcinoma	1.0	1.5	(-)	(-)	(-)
12. Breast adenocarcinoma	0.5	1.5	(-)	(-)	(-)

13. Breast adenocarcinoma	1.0	0.5	All (+) for coag. pos. hemolyt. staph.	All (+) for coag. pos. hemolyt. staph.	All (+) for coag. pos. hemolyt. staph.
14. Breast adenocarcinoma	1.5	0.5	All (+) for coag. pos. hemolyt. staph.	All (+) for coag. pos. hemolyt. staph.	All (+) for coag. pos. hemolyt. staph.
15. Breast adenocarcinoma	0.0	0.0	(-)	(-)	(-)
16. Breast adenocarcinoma	62.0	1.0	All (+) for coag. pos. hemolyt. staph. and alpha hemolyt. strep.	All (+) for coag. pos. hemolyt. staph. and alpha hemolyt. strep.	All (+) for coag. pos. hemolyt. staph. and alpha hemolyt. strep.
17. Breast adenocarcinoma	59.5	1.0	All (+) for coag. pos. hemolyt. staph. and alpha hemolyt. strep.	All (+) for coag. pos. hemolyt. staph. and alpha hemolyt. strep.	All (+) for coag. pos. hemolyt. staph. and alpha hemolyt. strep.
18. Breast adenocarcinoma	0.0	0.0	(-)	(-)	(-)
19. Breast adenocarcinoma	1.0	0.0	(-)	(-)	(-)
20. Breast adenocarcinoma	50.0	0.0	All (+) for coag. pos. hemolyt. staph. and beta hemolyt. strep.	All (+) for coag. pos. hemolyt. staph. and beta hemolyt. strep.	All (+) for coag. pos. hemolyt. staph. and beta hemolyt. strep.
21. Breast adenocarcinoma	55.5	0.0	All (+) for coag. pos. hemolyt. staph. and beta hemolyt. strep.	All (+) for coag. pos. hemolyt. staph. and beta hemolyt. strep.	All (+) for coag. pos. hemolyt. staph. and beta hemolyt. strep.

\* AZ hybrid strain having transplants from A mice with spontaneous tumors. The A mice originally belonged to the colony of Dr. J. J. Bittner.

\* The initial outflow times were in the range 110-120 seconds and complete hydrolysis of the substrate reduced this time to 40-45 seconds.

which were directly contaminated with bacteria, significant hyaluronidase action was observed.

Data in Table 7 includes results on adenocarcinomas of the breast in 11 mice. It is clear that the enzyme was present in the tumor tissue of 4 of the 6 with

TABLE 8

*Statistical analysis of the mean value of hyaluronidase inhibitor in A/ml. of normal, benign, and cancerous serum*

	NO. CASES	MEAN	STAND- ARD DEVI- ATION	DEVI- ATION FROM NORMAL	STAND- ARD ERROR OF DEVI- ATION	P	DEVI- ATION GROUP 4 FROM GROUP 3	STAND- ARD ERROR OF DEVI- ATION	P
1 (normal).....	90	16.2	5.4						
2 (benign).....	15	18.6	8.6	2.4	2.3	0.32			
3 (cancerous, nonmetastatic)...	70	24.1	7.8	7.9	1.1	<.001			
4 (cancerous, metastatic).....	80	38.4	14.7	22.2	1.8	<.001	13.8	1.9	<0.001

TABLE 9

*Mean hyaluronidase inhibitor values in A/ml. serum arranged according to primary site of malignant growth*

SITE OR TYPE	NONMETASTATIC		METASTATIC	
	Number	Mean	Number	Mean
Skin and mucous membrane.....	9	23	2	36
Esophagus.....			2	41
Stomach.....	4	24	17	40
Colon and rectum.....	7	20	6	35
Ovary.....	2	32	4	58
Cervix.....	31	26	12	40
Endometrium.....	7	23	3	35
Breast.....	7	23	10	31
Prostate.....	1	20	2	26
Bladder.....	1	25	3	35
Hypernephroma.....			1	50
Carcinomatosis.....			6	38
Parotid.....	1	13		
Sarcoma.....			3	33
Melanosarcoma.....			3	42
Lymphoblastoma.....			5	39
Multiple myeloma.....			1	27

demonstrable contamination but absent in the others and in the 5 sterile extracts. It was concluded that neither benign nor malignant tumor tissues have any hyaluronidase activity unless it is contributed by microorganisms which have the enzyme.

While hyaluronidase is not characteristic of malignant cells, the blood serum of patients with cancer has an abnormally high concentration of hyaluronidase

inhibitor. In our first study of this change the data in Tables 8 and 9 were obtained (16), from which it follows that the degree of inhibitor elevation is significantly greater in the more involved cases with metastases than in the non-metastasized malignancies. Benign tumors were accompanied by no change in the inhibitor level. It may be noted that the old A value was used to express inhibition at that time. Subsequently, confirmatory evidence was obtained as illustrated in Table 10, in which the values are given as per cent inhibition (14). It should be pointed out that this latter data includes a non-metastatic group with a mean not different from the normal, but in these cases the majority of the lesions were small and localized, and the elevation of the inhibitor is manifest

TABLE 10

*Summary of the mean values of per cent inhibition by normal, benign, and cancerous sera*

GROUP	NO. OF CASES	MEAN	STANDARD ERROR OF MEAN
Normal .....	75	21	$\pm 1.0$
Benign.....	25	23	$\pm 1.2$
Malignant (non-metastatic).....	30	22	$\pm 1.2$
Malignant (with metastases).....	32	36	$\pm 1.0$

TABLE 11

*Per cent inhibition of hyaluronidase by serum of patients with benign lesions*

SITE AND TYPE OF LESION	NO. CASES	MEAN
Breast*.....	10	24
Leukoplakia of tongue.....	1	30
Lipoma .....	2	28
Granuloma of ear.....	1	28
Chronic stasis ulcers.....	3	20
Chronic duodenal ulcers.....	7	27
Xeroderma pigmentosa.....	1	21

\* Including fibromas, fibrocystic disease, gynecomastia, and intraductal papillomas.

only when the disease has progressed to the stage of a systemic reaction. A breakdown of the data in Table 10 is given in Tables 11 and 12.

It might be added that in a study of the relationship of the serum inhibitor to the incidence of mammary cancer in mice, which was carried out with Dr. J. J. Bittner of the Division of Cancer Biology, and with Mr. T. A. Good (17), no significant difference was found between individuals with and without the milk agent which determines the incidence of mammary cancer. Neither was a significant difference found between those with and without tumors. A tendency was observed for the inhibition titer to vary inversely with the strain incidence of mammary cancer in the A, Z, and AZF<sub>1</sub> mice. What significance can be attached to these findings remains to be seen.



## TISSUE DESTRUCTION

In looking for some common denominator that might account for the observed elevations of the serum inhibitor in the diverse conditions already mentioned, it occurred to us that tissue destruction might be an etiological factor. This point of view was given some credence when, with Dr. E. Y. Hakanson, it was found that a remarkable increase in the serum inhibitor occurred in women after parturition, the peak being noted from the second to fifth day post-partum (18). A tendency to elevated inhibitor concentrations was also observed during menstruation.

TABLE 12

*Per cent inhibition of hyaluronidase by serum of patients with malignant tumors*

PRIMARY SITE OF TUMOR	NON-METASTASIZED		WITH METASTASES	
	No. Cases	Mean	No. Cases	Mean
Breast adeno or scirrhus carcinoma . . . . .	4	25	11	33
Oral and lip carcinoma . . . . .	5	21	5	39
Stomach carcinoma . . . . .			5	36
Skin basal and squamous cell carcinoma . . . . .	7	20	1	40
Malignant melanoma . . . . .	2	15	1	47
Malignant myxoma . . . . .	1	24		
Rhabdomyosarcoma . . . . .	1	37		
Bronchogenic carcinoma . . . . .	1	15		
Parotid mixed tumor . . . . .	2	12		
Prostatic carcinoma . . . . .	1	33		
Lymphoblastoma . . . . .			3	57
Rectal adenocarcinoma . . . . .	2	23		
Hypernephroma . . . . .			1	60
Osteogenic sarcoma . . . . .			3	33
Thyroid carcinoma . . . . .	1	17		
Myosarcoma . . . . .	1	28		
Synovioma . . . . .			1	38
Testis carcinomatous mixed tumor . . . . .	1	30		
Carcinoma esophagus . . . . .			1	33
Neurofibromatosis with malignant degeneration . . . . .	1	33		

A direct approach to this problem was made in collaboration with Mr. T. A. Good and Drs. R. A. Good and V. C. Kelley. (Mr. Good is still a medical student, but he and certain others at the University of Minnesota have shown an impressive ability to carry on a surprising amount of mature research in spite of a heavy student load.) Tissue destruction was produced in laboratory animals by ferric chloride sterile abscesses in the skin and electrocautery of the back muscles. A significant increase in the serum inhibitor resulted (19), and the same effect was obtained in rabbits from whole body X-irradiation (20). That tissue destruction was only one instigating factor of a more fundamental effect that influenced the serum inhibitor appeared from subsequent work which will be taken up later.

## OTHER DISEASE STATES

Basic questions, such as the nature and anatomical origin of the non-specific serum inhibitor, have concerned us for some time. Jointly with Dr. D. H. Moore of Columbia's College of Physicians and Surgeons we investigated the inhibitor in electrophoretically separated fractions of human serum and found it to migrate chiefly with the albumin (21). Later with Dr. L. W. Wattenberg, who was still a medical student at the time, we examined a wide variety of tissues in the rabbit for the inhibitor and found it in none of them (2). Our studies are continuing in this direction.

There is the possibility that some organ, such as the liver, may produce the inhibitor but lose it to the blood as fast as formed so that it cannot be detected in the tissue itself. In order to determine whether the liver was involved with the inhibitor, a study of it in liver diseases was carried out with Dr. G. G. Snively

TABLE 13  
*Correlation of Hyaluronidase Inhibitor with Liver Function Tests*

MEASUREMENT	NO. CASES	COEFFICIENT OF CORRELATION (r)	P
Alkaline phosphatase.....	40	0.88	<0.001
Total cholesterol.....	46	0.58	<0.001
Bromsulfalein.....	44	0.54	<0.001
Bilirubin.....	58	0.78	<0.001
Total protein.....	48	0.07	0.6
Cephalin flocculation.....	75	0.11	0.3
Thymol turbidity.....	59	0.74	0.2
Urinary urobilinogen.....	63	0.20	0.8
Cholesterol ester.....	46	0.12	0.4

of the Dept. of Medicine (22). A definite correlation was found between the serum inhibition and both the clinical course and several laboratory tests of liver function, *i.e.*, serum alkaline phosphatase, bilirubin, total cholesterol, and bromsulfalein retention. Other liver function tests showed no significant correlation, Table 13. Actual mean values may be seen in Table 14 for comparison to a large series of normals with a mean per cent inhibition of  $21.5 \pm 0.7$ . It was noted that in several cases of severe hepatic coma, the previously elevated values fell to subnormal in the very terminal stages. This suggests the speculation that the integrity of a certain amount of hepatic function is required for the development of both normal and elevated levels of the serum inhibitor.

Continuing this use of disease as a tool for the understanding of the physiological mechanisms of the hyaluronidase inhibitor, an investigation of changes in children with active lipid nephrosis and with acute glomerulonephritis was undertaken with Drs. V. C. Kelley and R. A. Good of our Pediatrics Dept. (23). In 20 cases of active lipid nephrosis the mean per cent serum inhibition was found to be  $48 \pm 2.3$ , practically double the normal. In 7 cases of acute glomerulonephritis the mean was  $43 \pm 3.3$ , also greatly elevated with respect to normal,

and in 5 children convalescing from this disease the mean was  $19 \pm 1.3$ , slightly lower than the normal.

At about this time we began to examine our results in the light of the recent findings on conditions of stress, and the role of adrenocorticotrophic hormone (ACTH) and cortisone. This led to a new conception of the possible mechanism of the serum inhibitor changes that might offer an explanation of the observations in these various and diverse syndromes.

TABLE 14  
*Hyaluronidase Inhibition by Sera of Patients with Liver Disease*

DISEASE	NO. CASES	MEAN % INHIBITION $\pm$ STD. ERROR OF MEAN
<i>Cirrhosis</i>		
With alcoholic history.....	21	$52 \pm 3$
Without alcoholic history.....	4	$40 \pm 5$
<i>Viral Hepatitis</i>		
Infectious hepatitis.....	8	$48 \pm 4$
Homologous serum hepatitis.....	9	$43 \pm 3$
Infectious mononucleosis.....	5	$42 \pm 3$
<i>Miscellaneous</i>		
Chronic cholangitis.....	1	67
Carbon Tetrachloride poisoning.....	1	94
Primary cholangiolitic cirrhosis.....	2	69

TABLE 15  
*Effect of Injection of ACTH in Children on the Serum Hyaluronidase*

TREATMENT	NO. CASES	% INHIBITION	
		Mean	Std. Error of Mean
Before ACTH.....	5	22	2.0
After ACTH inj. for 4 days (9mg.q.6h.).....	5	34	2.0
7 Days after last inj.....	2	19	1.0

#### STRESS AND ADRENAL ACTIVITY

Last summer, in collaboration with Mr. T. A. Good and Drs. R. A. Good and V. C. Kelley, we were fortunate enough to obtain sera from 5 children suffering from hypoglycemia who were being treated with injections of 9 mg. of ACTH every 6 hours over a 4 day period in connection with a study by Drs. I. McQuarrie, E. G. Bauer, W. S. Wright and M. R. Ziegler. It was found that the ACTH produced a significant rise in the serum inhibitor which reverted to slightly below the preinjection level 7 days after the administration of the hormone was terminated, Table 15, (19).

This effect of adrenal stimulation led to further investigations of conditions that could be considered to be stress phenomena (19). Accordingly, Arthus and Shwartzman phenomena in rabbits were studied. Anaphylactic shock in rabbits

had been found earlier (7) to have no consistent effect on the inhibitor and this was confirmed by subsequent experiments included with those on the Arthus and Shwartzman phenomena. In Table 16 it may be seen that these phenomena resulted in significant elevations in the inhibitor. The same result was obtained by the induction of serum sickness through intravenous injections of horse serum. A similar effect was found on chilling rabbits, Table 17, and in order to determine whether the adrenal was involved, the effect of adrenalectomy on rats was studied, Table 18. The control operated animals were subjected to the surgery without removal of the adrenals, as a check on the effect of the operation

TABLE 16

*Effect of Sensitization Reactions in Rabbits on the Serum Hyaluronidase Inhibitor*

	TIME OF SAMPLING	NO. CASES	% INHIBITION	
			Mean	Std. Error of Mean
Arthus Phenomenon	Before Inj.	11	14	1.3
	3 days after inj.	11	25	2.0
Shwartzman Phenomenon	Before Inj.	10	16	1.1
	24 hrs. after	9	28	2.3
	I. V. Inj.			
Normals		11	16	0.5

TABLE 17

*Effect of Chronic Chill in Rabbits on the Serum Hyaluronidase Inhibitor*

TREATMENT	TIME BLOOD OBTAINED	NO. CASES	% INHIBITION	
			Mean	Std. Error of Mean
Chronic chill in 40°C room (serial detns. in same animals)	Pre-chill	6	16	1.0
	After 3 days in cold room	6	18	0.6
	After 5 days in cold room	6	24	1.1
	7 Days after termination of chill	6	17	0.5

itself. From these still meager data it appears that adrenalectomy abolishes the rise in the serum inhibitor that is normally caused by chilling. More data of this nature are being collected, and it would be rather impetuous at this time to make positive statements, but the present indications are that the adrenal cortex may play an essential role in mediating the fluctuations in the serum inhibitor concentration that occur in the wide variety of conditions that have been discussed.

In summing up it should be emphasized that the elevation of the non-antibody hyaluronidase inhibitor of the blood serum that has been observed in infectious diseases, cancer, and liver and kidney diseases, when these are advanced to the point of systemic involvement, may prove to be one of the adrenal-mediated



reactions to stress. Regardless of the mode of action, it would appear that the inhibitor response may be a defense mechanism to counter the invasiveness of microorganisms, and that the quantitation of this response might be of value in certain areas of medical practice. In any case, the elucidation of the nature and action of this blood factor can be expected to yield information that will find its place in the practical matters with which the physician must be concerned.

A gratifying feature of these studies has been the effective collaboration of a group of individuals with diverse backgrounds, and whatever accomplishment has been attained can be ascribed to this blending of efforts. It has meant that we in physiological chemistry have joined forces with others from various clinical fields as well as from the other basic medical sciences, not only in our own, but in other institutions as well.

If I may make a statement of my point of view—It is the proper antidote, I believe, to the scientist's inevitable increasing specialization, which tends to direct his attention into ever-narrowing channels, that collaboration between

TABLE 18

*Effect of Chronic Chilling and Adrenalectomy on Serum Hyaluronidase Inhibitor of Rats*

TREATMENT	NO. CASES	% INHIBITION	
		Mean	Std. Error of Mean
Adrenalectomized . . . . .	5	17	0.6
Adrenalectomized (Chilled). . . . .	16	19	0.7
Mock Operated . . . . .	5	23	1.6
Mock Operated (Chilled). . . . .	8	28	2.0
Normals . . . . .	20	22	0.6
Normals (Chilled). . . . .	5	33	1.0

those with diverse skills and abilities be emphasized. For the most part, we are individualists, and pretty rugged at that—and I happen to think this is good. However, it is nonsense to assume that we must work only in beauteous isolation to preserve our individualism. Collaboration need not be at the expense of the individual's independence of thought and activity, but it can be, and should be, a free and voluntary cooperation in which each contributes within his capacities as he sees fit. Of course, this demands on the part of the individual a recognition that the development of knowledge is more important than his own personal whims—that he may, in fact, be able to make the greater contribution as part of a congenial team than he can alone, and that in any case, he must humbly bend to the demands of his work as they arise. He must not take himself too seriously, he must be able to smile at himself; in short, he must have a sense of humor. We are not here long to carry our burdens and present our gifts, and the body of knowledge to which we make a few additions is the important thing—not we who play with the glassware.

The point that it is seldom practical, or even possible, for a single individual to develop to a significant degree in a variety of disciplines, and that generally

he is happy to confine himself to a measure of accomplishment in just his own field, is brought out in a story that Prof. Linderström-Lang told me last summer in Copenhagen, and with this story I shall conclude.

It appears that a renowned oculist was to sit for the painting of his portrait by one of our surrealist artists, and during the painting the artist would not allow his subject to see what he was doing. When the painting was finally completed, the artist swung the easel around and asked the oculist what he thought of it. The oculist saw before him a huge eye almost filling the entire canvas, and in one small corner, there was his portrait. He was flabbergasted, but when he found voice he said, "Thank heavens that I am not a proctologist!"

### ADDENDUM

After the manuscript of the present paper was submitted for publication, further studies in collaboration with Dr. B. Sylvén of the Cancer Research Division of Radiumhemmet, Karolinska Sjukhuset, Stockholm, Sweden, and with Dr. L. W. Wattenberg and Miss M. J. Ochs in our laboratory, yielded considerable evidence to indicate that the non-specific hyaluronidase inhibitor of blood serum is a complex of heparin, polypeptide and lipid which is electrophoretically homogeneous. These studies will appear elsewhere. With Drs. F. H. Adams, V. C. Kelley, and P. F. Dwan (Pediatrics, in press) an investigation of the effect of ACTH treatment of rheumatic patients revealed that the abnormally high serum inhibitor levels characteristic of the disease were brought down to normal during treatment, but reverted to high values when the therapy was discontinued. Meanwhile similar studies by Dorfman and Moses (Proc. Soc. Exp. Biol. Med., 73:667, 1950), Hakanson and Luft (Acta. Endocrinol., 3:318, 1949) and Schmith and Faber (Acta Endocrinol., 3:310, 1949) have appeared.

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## THE WILLIAM HENRY WELCH LECTURES

### BACTERIOLOGICAL ASPECTS OF THE PATHOGENESIS OF TUBERCULOSIS\*

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#### *The effect on tissue cells of tubercle bacilli and their products*

When cultures of tissues taken from normal animals are inoculated *in vitro* with virulent tubercle bacilli, an apparently symbiotic relationship becomes established between the bacterial and mammalian cells (31, 4). The bacilli are rapidly phagocytized but continue to multiply and are soon found in enormous numbers within the phagocytes, which also continue to increase in number. Under these conditions, both types of cells retain a healthy appearance for prolonged periods of time, as if they were indifferent to each other's presence; moreover, the symbiotic relationship between bacilli and phagocytes can be maintained through several subcultures *in vitro* by inoculation into new medium. Thus, tissue culture studies provide no evidence that virulent tubercle bacilli exert any obvious cytotoxic effect on phagocytic cells, or that the latter have any significant inhibitory effect, in the absence of humoral factors, on the multiplication of the bacilli that they have phagocytized. Similar conclusions have been derived from histological studies of the early response elicited by the injection of virulent tubercle bacilli into the skin of normal animals (27, 30). For a few days, the bacilli multiply freely without calling forth any striking reaction beyond that caused by the trauma of injection; they behave as almost inert intracellular parasites. It is only after 10-15 days that the lesion takes on a more characteristic aspect when inflammation begins to develop. Even with large infective doses, tubercle formation and caseation require a minimum of two weeks before becoming evident.

The course of the initial tissue reaction is dramatically different when living tubercle bacilli or their breakdown products are injected into tuberculous animals or into animals that have been rendered specifically hypersensitive (27, 30). In this case, the bacillary materials immediately behave as powerful poisons. They elicit at the site of injection an acute exudative response which goes on rapidly to the development of productive tubercles and to caseation, the whole process taking place within two to four days. The necrotic effect of bacillary products on hypersensitive tissue can be recognized not only by injection into the whole animal but also *in vitro* by means of tissue culture experiments. Cultures of cells taken from tuberculous or hypersensitive guinea pigs are either killed or their migration and proliferation inhibited by the addition to the medium of tuberculin in concentrations so small as to be innocuous for the cells taken from normal animals of the same species (31, 26).

\* Delivered at the Blumenthal Auditorium, The Mount Sinai Hospital, New York, on March 14, 1950.



The facts outlined in the preceding paragraphs have given rise to the view that the tuberculous lesions result from the peculiar necrotoxic effect of tuberculin-like substances on tissues rendered hypersensitive to the latter by prior contact with tubercle bacilli. However useful, this concept does not seem sufficient to explain some of the aspects of the pathogenesis of tuberculosis, for it has been established that true tubercle bacilli which have lost on subculture in artificial media the ability to cause progressive disease in susceptible animals—in other words, which have become avirulent or, at least, attenuated—still retain the ability to induce the tuberculin positive state in normal animals and to elicit a typical tuberculin reaction in hypersensitive animals. In consequence, one may conclude that, although tuberculin allergy certainly contributes to the pathological picture of tuberculosis, it does not account for the ability of the virulent forms of tubercle bacilli to initiate progressive and fatal disease.

In the hope of obtaining information concerning the bacillary constituents or properties responsible for pathogenic behavior, a comparative study has been undertaken in our laboratory of strains of tubercle bacilli endowed with different degrees of virulence. Fortunately, there are available a variety of strains of mycobacteria possessing definite characteristics with reference to pathogenicity. For the sake of convenience, these strains can be classified as follows:

a) the fully *virulent* forms capable of causing progressive disease in normal animals of susceptible species.

b) the *attenuated*<sup>1</sup> forms which have lost the ability to cause progressive disease although they are still able to give rise to a limited degree of multiplication *in vivo*, producing lesions that heal spontaneously after a few weeks to a few months. Representative of this group is the human strain R<sub>1</sub>Rv, which rapidly lost virulence for normal animals during cultivation on artificial media, but which is still capable of causing caseation and death in silicotic guinea pigs (18, 34). To this group also belongs the classical BCG, an attenuated strain of bovine type widely used for immunization against tuberculosis (5).

c) the *avirulent*<sup>1</sup> variants, also derived from virulent forms but which have become totally incapable of multiplying *in vivo*. Representative of this group are the cultures H37Ra, JH16Ra and R<sub>1</sub>Ra isolated at the Trudeau Sanatorium (28).

d) the saprophytic strains which grow rapidly on ordinary culture media and are not derived from virulent cultures.

#### *The correlation between bacterial morphology and virulence*

The search for characteristics that might be correlated with virulence was first centered on a pair of cultures of the human strain H37: H37Rv (virulent) and H37Ra (the avirulent variant) (35). In confirmation and extension of earlier findings, striking differences were soon recognized between the manner of growth

<sup>1</sup> The BCG culture is often referred to as "avirulent." Its properties correspond rather to those of the "attenuated" strains which, according to Pasteur's original definition, are capable of giving rise to a self-limited immunizing infection, but not to fatal disease. We prefer to use the adjective "avirulent" for the variant forms which, like H37Ra, appear unable to multiply *in vivo*.

of these two forms (25). The bacilli in cultures of H37Rv tend to adhere to one another in the direction of their long axis, thus forming long strands giving to the young growth a serpentine pattern which spreads as a veil over the surface of solid or liquid oleic acid-albumin agar (Figure 1). Further comparison of various cultures of tubercle bacilli has led to the hypothesis that a correlation exists between morphological characteristics and virulence. All fully virulent forms (either laboratory strains or cultures isolated from pathological specimens) exhibit the serpentine pattern of growth, whereas all cultures tested thus far which grow in an unoriented manner in oleic acid-albumin media have been



FIG. 1

Left: Ziehl-Neelsen stained preparation of an 8-day-old culture of avirulent tubercle bacilli (H37Ra), grown in oleic acid-albumin medium. The bacilli are not oriented and form clumps.  $\times 1520$ .

Right: Ziehl-Neelsen stained preparation of virulent tubercle bacilli (H37Rv), grown in oleic acid-albumin medium. The bacilli form serpentine strands.  $\times 1520$ .

found to be avirulent (29). The attenuated strains (BCG in particular) are somewhat intermediate in morphology (Figure 2) (25, 11). However, it will be emphasized later that this statement is not entirely valid in the case of cultures belonging to the attenuated group since several of these exhibit a serpentine pattern of growth indistinguishable from that of the fully virulent forms.

On the basis of indirect evidence—for example, of the fact that addition to the culture medium of certain wetting agents prevents the virulent tubercle bacilli from growing in an oriented manner (25, 12)—it appeared likely that the serpentine pattern of growth was due to the presence around the bacteria of a hydrophobic lipid causing the individual cells to adhere to one another in the direction of their long axis. This hypothesis has been substantiated by the discovery that

the typical strands of virulent tubercle bacilli can be rapidly dispersed into their individual component cells, even at low temperature, by treatment with a variety of hydrocarbons, such as petroleic ether (2). It is of particular interest that disintegration of the bacillary strands can be achieved without affecting the stain-

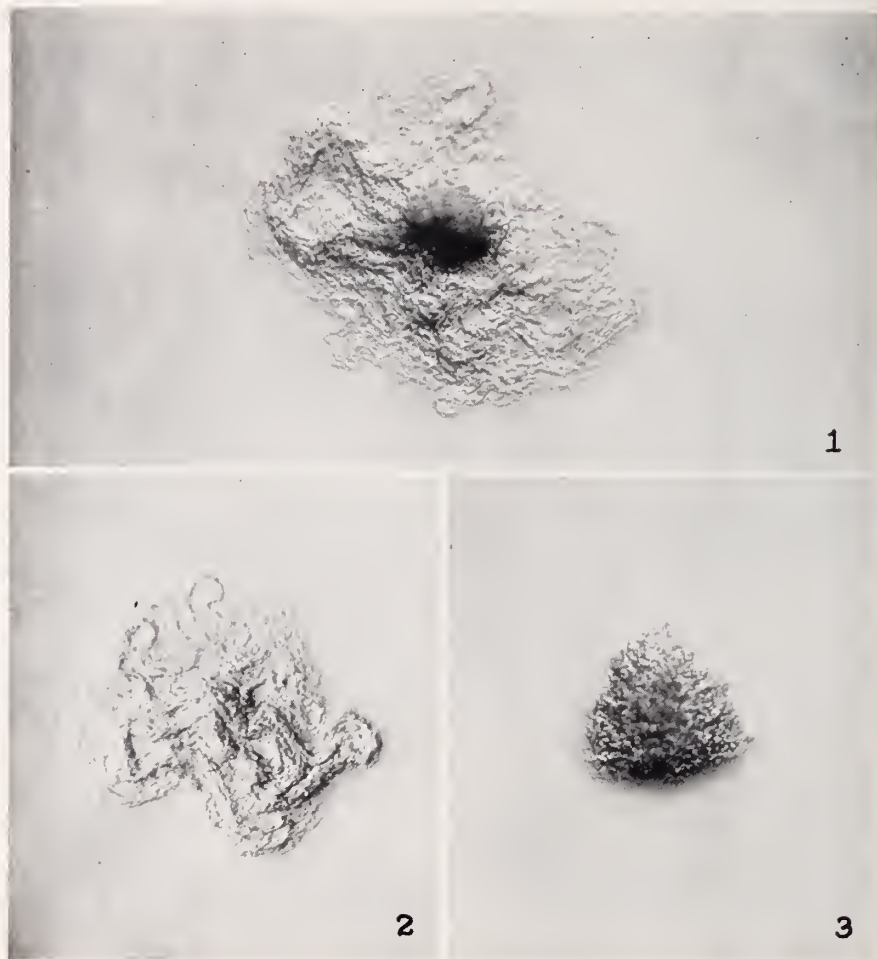


FIG. 2

Comparative colonial morphology of three strains of tubercle bacilli: 1) BCG (strain obtained from the Henry Phipps Institute) 2) H37Rv (virulent human strain) 3) H37Ra (avirulent variant of H37Rv).

All colonies are from a 9-day growth on oleic acid-bovine albumin agar.  $\times 230$ .

ing characteristics and the viability of the bacilli, a fact which suggests that the lipid responsible for the serpentine pattern is not an essential part of the bacillary structure but merely exists as an outer layer of the cell.

Little is known of the role played by this lipid in the pathogenesis of tuberculosis. It has been shown recently that the cells—living or dead—of virulent

tubercle bacilli can inhibit the migration on coagulated plasma of the phagocytes that have engulfed them; by contrast, the avirulent variants are much less active in modifying the rate and extent of leucocytic migration even though they are as readily phagocytized as their virulent counterparts (1, 21). Moreover, there appears to exist a certain correlation between the susceptibility of a given animal species to a given type of tubercle bacilli (mammalian or avian) and the susceptibility of the cells of this species to be inhibited in their migratory activity by the corresponding bacillary type. Thus, avian bacilli inhibit the migration of avian (but not of guinea pig) leucocytes, whereas mammalian bacilli affect the leucocytes of the guinea pig but not those of the chicken. It is of considerable interest, therefore, that when the lipid fraction released from virulent mammalian tubercle bacilli by extraction with petroleic ether is adsorbed on otherwise inert particles, it confers upon them the ability to inhibit the migration of guinea pig leucocytes (2). Mention should also be made of the fact that repeated injections into mice of small amounts of this crude lipid resuspended in oil brings about vascular pulmonary lesions and death of the animals after a period of nine days or longer. The same fraction, however, appears entirely non-toxic for mice when injected as a single dose, even in large amounts.

Because of the fragmentary and preliminary nature of these findings, it is difficult to evaluate, at the present time, their significance in the pathogenesis of tuberculosis. On the one hand, the fraction of tubercle bacilli obtained by simple extraction with petroleic ether constitutes a mixture of several substances, and it will be necessary to determine the biological activities of each one of them. On the other hand, cultures of BCG and of a saprophytic mycobacterium, as well as brain tissue, extracted with petroleic ether under the conditions used for extraction of virulent tubercle bacilli, have also yielded a lipid fraction capable of killing mice (2). It is possible that these extracts of attenuated bacilli and of tissue cells merely exert a non-specific toxic effect which bears no relation to the lethal effect obtained by the repeated injection of extracts of virulent tubercle bacilli, but no convincing data exist to support this view. Neither is any knowledge available of the amount and activity of the lipid produced by attenuated bacillary strains in comparison with that produced by fully virulent strains. For these reasons it is not yet possible to evaluate accurately the relation of this interesting bacillary material to the pathogenic behavior of tubercle bacilli.

#### *Determinants of virulence*

The observations reported so far appear to suggest some correlation between the serpentine pattern of growth of tubercle bacilli and their pathogenic activity, but it is also true that the virulent and avirulent forms differ in many characteristics other than the morphological appearance of their growth. A few of these differences may be listed here.

The avirulent variants (H37Ra, JH16Ra and R<sub>1</sub>Ra) are much less acid-fast than the virulent and attenuated strains. Indeed, these Ra forms are essentially non-acid-fast when growing as submerged colonies in a soft agar (0.1%) medium containing glucose (8). Whereas all strains that exhibit the serpentine pattern



of growth are able to bind the dye neutral red in the form of its red salt even in strongly alkaline media (sodium barbiturate or 0.1 N NaOH), the Ra forms allow the dye to become yellow under the same conditions (13, 14). In comparison with the virulent forms from which they are derived, the avirulent variants are usually more difficult to cultivate in synthetic as well as in organic media; they appear to have more exacting nutritional requirements and to be more susceptible to the toxic effect of certain organic acids and of  $Zn^{++}$  and  $Mn^{++}$  ions. On the other hand, they are better able than the virulent forms to reduce methylene blue in dehydrogenase experiments of the Thunberg type (3) and are more resistant to the growth inhibitory effect of d-serine (9). Some of these differences may be merely different manifestations of the same fundamental character, but it is also possible that a few correspond to independent variations. In any case, it is likely that the loss of the serpentine pattern of growth (and of the ability to produce the particular lipid mentioned earlier) constitutes only one of the many alterations in cellular structure and properties that occur when tubercle bacilli change from the mode of growth typified by the H37Rv (virulent) form to that typified by H37Ra.

A consideration of some of the characteristics of attenuated cultures may help in analyzing which one of these alterations are of significance in pathogenic behavior. The human strain R<sub>1</sub>Rv, which has become unable to produce progressive disease in guinea pigs (18, 34) still continues to grow in the form of serpentine strands indistinguishable from those produced by the fully virulent strains; similarly, it is possible to isolate from the attenuated bovine strain BCG, substrains giving the typical serpentine pattern of growth in oleic acid-albumin medium (36) but like R<sub>1</sub>Rv unable to cause fatal infection. How are these facts to be reconciled with the hypothesis that the serpentine pattern of growth is the earmark of the virulent forms? Several possibilities come to mind.

One might assume that the various bacillary strains differ in the amount of specific lipid that they produce. According to this hypothesis, R<sub>1</sub>Rv and BCG, for example, would produce less of it than the fully virulent forms—but still enough to cause the bacilli to adhere one to the other in the direction of their long axis. This amount would not be sufficient to allow maximum virulence but would permit a certain extent of multiplication *in vivo*.

It is also possible that there exist qualitative differences in the characteristics of the specific lipids produced by the various strains of mycobacteria and that R<sub>1</sub>Rv and BCG produce substances inefficient in endowing these cultures with virulence.

Finally, one may consider that loss of virulence can result from alterations unrelated to the production of serpentine strands but affecting by entirely different mechanisms the ability of the bacilli to multiply or survive *in vivo*. This hypothesis is supported by quantitative bacteriological studies of the fate of tubercle bacilli of various degrees of virulence injected into normal animals. It has been found that the avirulent forms (H37Ra) are rapidly destroyed and probably never multiply *in vivo*; whereas the attenuated strains (R<sub>1</sub>Rv and BCG, for example) seem at first to multiply at the same rate as the fully virulent strains.



After a certain length of time, however, their multiplication stops instead of continuing long enough to produce progressive disease as is normally the case with the virulent strains. These findings suggest that, under the conditions of the experiment, there come into action within one or two weeks after infection certain processes which are capable of inhibiting the growth of the attenuated forms but which are much less effective against the fully virulent forms. These growth inhibitory processes have not yet been identified, but it appears likely that they fail to function at the site of lesions produced by silica dust.

Silicosis enhances the susceptibility of man to tuberculosis. Similarly, silica dust introduced by subcutaneous injection or by inhalation into guinea pigs or mice produces local conditions which also favor the multiplication, not only of virulent but also of attenuated tubercle bacilli, rendering the latter capable of causing caseation, cavitation and death (7, 20, 17, 37). Enhancement of infection by silicosis is not due to an increase in the intrinsic virulence of the infective agents, for the cultures recovered from silicotic lesions exhibit the original level of virulence characteristic of the culture injected into the silicotic animal. For example, bacilli recovered from silicotic guinea pigs dying of tuberculosis caused by the R<sub>1</sub>Rv strain are unable to cause progressive disease in normal animals, and moreover, they remain localized in the tissues altered by the silica dust and do not give rise to generalized invasion. In other words, silicosis facilitates infection either by causing the local accumulation of substances that favor the growth of the bacilli, or by interfering locally with the mobilization or performance of the defense mechanisms which would otherwise hold bacillary multiplication in check. The problem seems to be sufficiently well defined in pathological terms to permit the experimental analysis of some of the physiological and immunological mechanisms which affect the local multiplication of tubercle bacilli *in vivo*.

*The inhibitory effect of certain naturally occurring organic substances on the growth of tubercle bacilli*

It has long been known that tubercle bacilli rapidly die when placed under anaerobic conditions *in vitro*, and recent experiments in our laboratory have shown that their viability is much decreased by the addition of 0.5 per cent glucose to the culture medium. On the other hand, histopathological observations suggest that the bacilli usually decrease in numbers at the site of inflammatory response and particularly in caseous material, whereas they begin to multiply at an enormous rate as soon as the caseous area opens into a bronchus (6). Although little is known of the biochemical environment prevailing within inflammatory and caseous areas, one may assume that it is partially anaerobic, a view supported by the fact that these areas are acidic (approximately pH 6.5), at least during certain phases of their evolution (23). Thus, the indirect evidence derived from observations concerning the survival and multiplication of bacilli *in vitro* as well as *in vivo* suggests that the establishment of an anaerobic environment may, under certain conditions, act as a protective mechanism retarding the spread of tuberculous infection. Since anaerobic metabolism usually

results in the production and accumulation of organic acids, it appeared worthwhile to investigate the effect of this group of substances on the growth of various strains of tubercle bacilli. A few of the results obtained in oleic acid-albumin media are summarized in Table I.

As anticipated from previous experience, the long chain fatty acids were found to inhibit the growth of tubercle bacilli, caprylic and capric acids being the most active in this respect. Unexpected, however, was the finding that even the short aliphatic saturated acids (acetic, propionic and butyric) also proved markedly inhibitory under the conditions of the test. Worthy of notice is the fact that the avirulent and attenuated strains so far tested have proven somewhat more susceptible than the virulent forms to the inhibitory effect of lactic acid, a common product of anaerobic metabolism.<sup>2</sup> It appears possible, therefore, that the inflammatory response to the presence of bacilli may result in the local production or accumulation of organic substances which, under certain conditions, can interfere with the progress of the disease.

TABLE I

*The effect of certain organic acids and of Zn Cl<sub>2</sub> on the growth of mammalian tubercle bacilli*

BACTERIAL STRAINS	MOLAR CONCENTRATIONS OF THE FOLLOWING SUBSTANCES REQUIRED FOR 50% GROWTH INHIBITION OF GROWTH			
	Butyric acid	Capric acid	Lactic acid	Zn Cl <sub>2</sub>
	<i>M</i>	<i>M</i>	<i>M</i>	<i>M</i>
Human Virulent (Amerzanga).....	0.0015	0.00001	0.008	0.0007
Human Attenuated (R <sub>1</sub> R <sub>v</sub> ).....	0.001	0.00001	0.005	0.0002
Bovine Virulent (Ravenel).....	0.003	0.00002	0.02	0.001
Bovine Attenuated (BCG P).....	0.0015	0.00002	0.007	0.00007
Bovine Attenuated (BCG T).....	0.003	0.00002	0.005	0.00015

#### *Antibacterial immunization against tuberculosis*

It is clear that, by increasing the variety of tests, one can recognize between virulent, attenuated and avirulent variants of mammalian tubercle bacilli many differences that appear unrelated; moreover, it has not yet been definitely established which of these differences are of significance in pathogenic behavior. It seems justified at the present time to state that all virulent cultures exhibit the serpentine pattern of growth in oleic acid-albumin media, whereas all cultures which, under the same conditions, grow without this type of orientation are avirulent. As there exist many mycobacteria that cannot cause progressive disease, although they do form serpentine strands, this morphological character is, at the most, a necessary but certainly not a sufficient condition of virulence. Vague and unsatisfactory as this statement is, it may nevertheless prove of some use in guiding the investigation of certain bacteriological problems of tuberculosis, for example, those pertaining to immunization with attenuated cultures or with bacillary extracts.

<sup>2</sup> As noted in Table I, there also exists a striking correlation between the virulence of different mammalian strains and their resistance to the growth-inhibitory effect of Zn Cl<sub>2</sub>.

It is generally agreed that the protective effect of BCG vaccination depends upon a limited but definite degree of multiplication of the BCG organisms in the tissues of the vaccinated host. One may assume, therefore, that the effectiveness of vaccination is affected in a certain measure by the factors which control the multiplication *in vivo* of the attenuated bacilli. The number of living cells in the vaccine is naturally of importance, and we have emphasized elsewhere the fallacy of expressing in mg. or cc. the amount of bacilli injected; the significant datum is not weight or volume of vaccine but the number of viable organisms, and it can be readily shown that different batches of BCG vaccine prepared by the classical technique differ enormously in their viability. It has been demonstrated also that one can obtain BCG cultures consisting in large part of living organisms, the viability of which remains unaltered for many weeks (10, 11, 16). But even when the quantitative factor of viability is controlled, the immunizing efficacy of various vaccine preparations may differ due to differences in the intrinsic level of attenuation of the cultures from which they are prepared.

Since all BCG strains stem from the culture of attenuated bovine bacilli obtained by Calmette and Guérin by prolonged cultivation in bile potato medium, it is generally believed that all BCG substrains are identical because of their common origin. However, comparative studies in our laboratory of four BCG cultures obtained from recognized collections in the United States leave no doubt that these strains differ markedly in many of their characteristics (cultural requirements, susceptibility to toxic agents, rate of autolysis, extent of the lesions produced in mice and in guinea pigs by the injection of equivalent numbers of living organisms). Even more important, perhaps, is the fact that BCG cultures are not homogeneous since each of them yields on oleic acid-albumin agar several colonial types. Indeed, it is possible to isolate at will from them subcultures which exhibit the serpentine pattern of the virulent strains and others which grow in the unoriented manner like the avirulent variants (36).

Much remains to be learned before one can evaluate the significance of these findings. It is necessary to know whether the various morphological types which occur in the BCG cultures differ in their ability to survive or multiply *in vivo*, and in their immunogenicity. Knowledge of these facts is naturally of importance for the standardization of BCG vaccination. Furthermore, it may lead eventually to the identification of the bacillary components or products that elicit the effective immune response and may facilitate the development of quantitative techniques for the evaluation of immune resistance and for the preparation of purified antigens free of bacterial cells to be used as immunizing agent in lieu of the living vaccine.

#### *The significance and mechanism of caseation necrosis*

We have considered thus far certain aspects of tuberculous infections which are in general terms common to all infectious diseases: the factors which affect the ability of the parasite to multiply *in vivo* and to cause damage, and the defense reactions by which the host attempts to restrain microbial invasion. There is an aspect in which the pathology of tuberculosis differs from that of other in-

fections, namely, caseation necrosis with its sequelae liquefaction and cavitation. This pathological process is probably responsible for some of the singular characteristics of tuberculosis.

Among infectious diseases, there are few in which the process of the microbial invasion can be retarded more readily than is the case with tuberculosis, but also there are none in which complete elimination of the infective agent is more difficult. Thus, physiological rest and the different forms of collapse therapy often succeed in retarding or even arresting the spread of tuberculosis, but these therapeutic measures rarely succeed in eradicating the tubercle bacilli from the established lesions. It is well known, furthermore, that animals infected with tubercle bacilli or immunized with BCG exhibit a much enhanced resistance to superinfection although they are usually unable to rid themselves of the bacilli present in a caseous area; in other words, immunity appears ineffective at the site of a caseous lesion. Similarly, chemotherapeutic agents like streptomycin or para-amino-salicylic acid are often capable of arresting and even sterilizing lesions in the exudative phase, but they are much less effective against the organisms present in the caseous areas; related to this, probably, in the fact that there exists a marked correlation between the rate of emergence of bacillary forms resistant to streptomycin and the extent of caseation at the time of treatment. Summarizing, one may say that certain physiological and immune mechanisms, as well as chemotherapeutic intervention, can retard or arrest the spread of the disease but are usually unable to eradicate the infection—a fact probably of great significance in the epidemiology of tuberculosis.

There is much evidence that the mortality of tuberculosis in the Western World began to fall early in the nineteenth century and has continued to fall at a steady rate ever since—reaching in 1950 one-tenth the level prevailing in 1850. This spectacular decrease in mortality would at first sight lead one to believe that complete eradication of the disease from our midst is only a matter of a few decades. There are, unfortunately, several observations that militate against this hope. It is true that only 30,000 persons died of tuberculosis in the United States during 1949, but in contrast there are probably a million persons in this country who harbor living tubercle bacilli and who excrete them in their sputa occasionally—or constantly. Most tuberculous patients become carriers—not only for short periods as in the case of other infectious diseases, but for their whole lifetime—thus constituting a huge reservoir of infection. It is obvious that, under present circumstances, no policy of segregation can succeed in removing this potential danger to the community and, as a result, morbidity rates are not falling at a rate comparable to that of the mortality rates (15). Many of the difficulties encountered in the eradication of tuberculosis—either from the individual or from society—have their origin in the fact that tubercle bacilli find in caseous areas a shelter against the defense mechanisms of the host and against chemotherapeutic agents. It is this situation which accounts in large part for the chronic character of the disease and for many of the therapeutic problems that it presents (6).

Unfortunately, caseation occurs very early in the tuberculous process, indeed,



so early that it is always present at the time of diagnosis. When first detected by clinical signs or on roentgenograms, most of the lesions of so-called "early" tuberculosis are, in reality, so advanced that they have undergone caseation necrosis (22). It would seem, therefore, as if total eradication of tuberculosis would be greatly facilitated by the development of more sensitive diagnostic techniques, capable of detecting the infection before caseation has set in. In principle, this problem does not appear insoluble for there have been developed recently immunological reactions of extreme sensitiveness which can reveal the presence of tuberculous infection. Thus, normal erythrocytes treated with certain extracts of tubercle bacilli are rendered specifically agglutinable by the serum of animals or of humans infected with tubercle bacilli (24), and clinical evidence is accumulating that the presence of the antibody responsible for this hemagglutination reaction is correlated with activity of the tuberculous process, thus constituting an index for its early detection (19, 32, 33, 33a). Theoretically, one might hope that refinement of immunological tests will render it possible to detect the very first phases of tuberculosis. Practically, however, this approach can hardly be of much use in permitting diagnosis before caseation has set in for recognition of the very first phase of incipient disease would demand that the test be performed on all individuals, systematically and at short intervals of time—a practical impossibility.

Can it be hoped that specific techniques will be developed to prevent or interrupt the progress of caseation? The biochemical processes which result in caseation necrosis, liquefaction and cavitation are so little understood that only the vaguest statements can be made concerning practical approaches to this problem. Caseous matter, it would seem, is produced when necrotic tissue fails to undergo the orderly and complete autolysis that would permit its resorption. Histopathological observations are compatible with the view that certain components of tubercle bacilli, or some products of their activity *in vivo*, are capable of interfering with one or several of the enzymatic reactions concerned in complete resolution. This working hypothesis appears amenable to experimental verification and offers challenging problems to immunologists and biochemists. Should its validity be established and should the biochemical systems involved in caseation and liquefaction be identified, it may become possible to influence in some degree the fate of necrotic tissue.

Because of the limitations of my training and experience, I have discussed almost exclusively some aspects of tuberculosis which can be analyzed in bacteriological, immunological and biochemical terms. There are, needless to say, many other aspects of the problem. I need only mention the beneficial effects of rest or of the different forms of collapse therapy to illustrate the fact that the response of man to infection with virulent tubercle bacilli can be profoundly altered by physiological factors—as yet unidentified. Even more obscure and, perhaps, more important, are the influences that brought about during the nineteenth century, in Western Europe and North America, a decrease in the prevalence and morbidity of tuberculosis long before there had been devised any



conscious prophylactic or therapeutic procedures, or measures of public health control, based on knowledge of the tubercle bacillus. Countless observations demonstrate that the course of tuberculosis is influenced by physiological, psychic and social determinants, thus making us aware of the multiplicity and variety of the reactions by which tubercle bacilli and tissue cells influence each other. It is this awareness which fosters the faith that tuberculosis can be controlled, not only by interfering with the multiplication and viability of the microorganisms in infected tissues, but also by exploiting the natural protective mechanisms whose effectiveness is so clearly suggested by epidemiological and clinical evidence.

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# THE EFFECTS OF THE SINGLE AND DOUBLE "TWO-STEP" EXERCISE TESTS UPON THE ELECTROCARDIOGRAMS OF 200 NORMAL PERSONS\*

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Normal electrocardiograms are frequently recorded in many persons despite a typical history of angina pectoris due to coronary arteriosclerosis and other causes. At rest, the coronary flow in such persons is apparently sufficient to supply the myocardial demand for oxygen, blood, and metabolites. It is only when additional work is imposed upon the heart that the demand for these substances exceeds the supply and symptoms and/or electrocardiographic alterations may occur.

The problem of diagnosing angina pectoris due to coronary arteriosclerosis is especially difficult when the history is atypical and the electrocardiogram is normal at rest. It is in this group particularly that the Master "2-Step" test (1, 2, 3) and Levy's "anoxemia" test (4) have been commonly employed as adjuvants in the determination of cardiovascular function. In the single "2-Step" test, the work of the heart is increased by having the patient perform a standard amount of work in the specific time of one and a half minutes. More recently, persons suspected of having coronary insufficiency despite a negative (1) response to the single "2-Step" exercise test have also performed twice the standard amount of work in three minutes. This modification of the single "2-Step" test was introduced in order to increase further the work of the heart and thus provoke electrocardiographic evidence of coronary insufficiency.

Although the effects of various degrees of exercise upon the electrocardiogram in normal persons have been determined by several investigators, the amount of exercise employed has varied widely, as have the methods for recording these changes. It is the purpose of the present report to record the electrocardiographic findings in an initial group of 200 normal persons who performed the Master single and double "2-Step" exercise tests.

## METHODS

Two hundred normal persons, comprising 95 males and 105 females varying in age from 17 to 57 years, are included in the present report. They were free of cardiac complaints, appeared healthy, and were normal on physical examination. Blood pressure determinations were not over 140/90 mm. of Hg. Fluoroscopic examinations, and standard and unipolar extremity and multiple precordial leads were within normal limits. Excluded from the study was any person with any chest complaint, however vague, or any history even remotely suggesting rheumatic fever or any other cardiovascular disorder. Most of the group were employees of The Mount Sinai Hospital, while the others were attending physicians.

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Each person was seen on two occasions, the second occurring at least 21 hours after the first. On the initial visit, a history was taken and the subject examined, fluoroscoped, and a 12 lead electrocardiogram recorded. The latter consisted of the 3 standard leads, aVR, aVL, aVF, and precordial leads V<sub>1</sub> to V<sub>6</sub>. Each person then performed the single "2-Step" exercise test, climbing the number of steps in one and a half minutes prescribed for his particular age, weight, and sex according to previously prepared tables (1). Immediately upon the completion of the exercise, standard leads I, II, and III, and unipolar lead V<sub>4</sub> or V<sub>5</sub> were taken and repeated 1, 2, and 5 minutes afterwards. All of the electrodes remained in place throughout the exercise test. On the second visit, standard leads I, II, and III, and unipolar lead

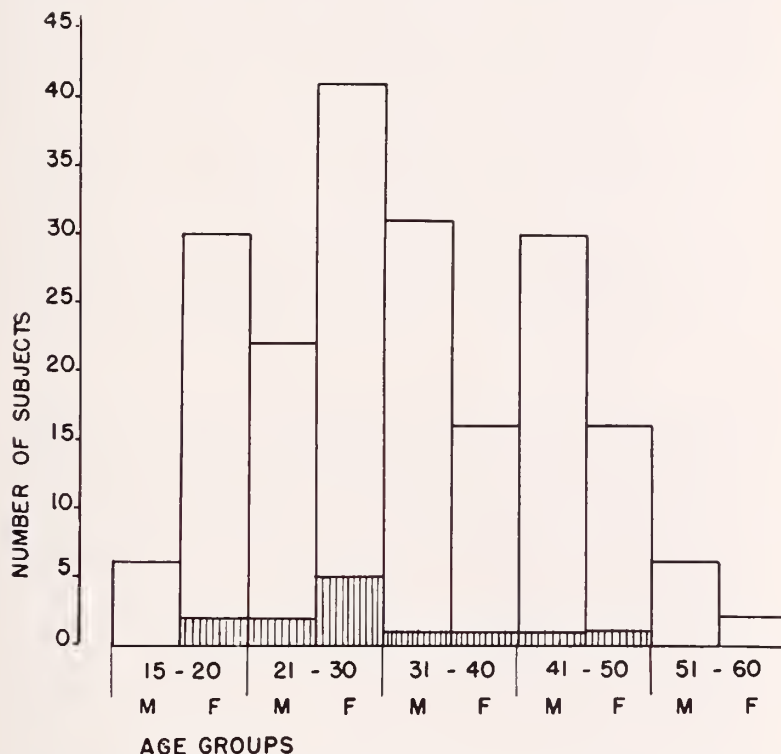


CHART 1. Age and sex distribution of the 200 persons included in this study. Shaded area indicates the number of persons in each group who had either a positive single or double "2-Step" test or both.

V<sub>4</sub> or V<sub>5</sub> were again recorded and the subject then performed double the original number of trips in three minutes. Records were taken subsequent to this test as after the performance of the single "2-Step" test. In no instance was pain elicited or did the test have to be discontinued because of dyspnea or inability to perform the required number of trips.

All electrocardiograms were taken on the direct writing Sanborn Visocardiette. Each record was analyzed for rate, RS-T segment deviation, P and T wave alterations, Q-T intervals, QRS complexes, and arrhythmias.

## RESULTS

1. *RS-T Segment Alterations.* In Chart 1 are recorded the age and sex distributions of the 200 persons included in the present study. Of these, 187 had electrocardiograms after the single and double "2-Step" exercise tests which showed no or minimal RS-T segment de-



pressions (i.e., 0.5 mm. or less in any lead). Twelve persons had RS-T segment depressions of 0.5 mm. to less than 1.0 mm. in one or more leads in either the single or double "2-Step"

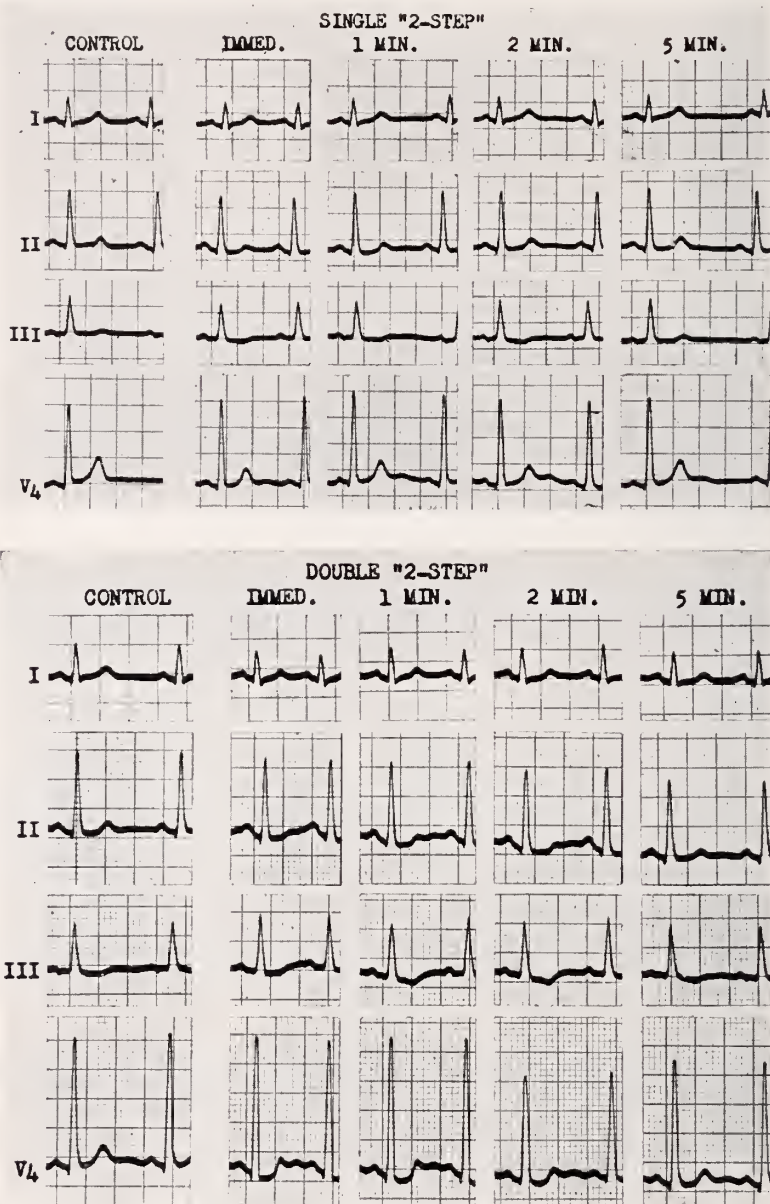


FIG. 1. B. K., 24 year old normal female. Single "2-Step" test negative. RS-T segment depressed in  $V_4$  immediately after double "2-Step" test.

exercise test, while one individual had an RS-T segment depression of 1.5 mm. after exercise. In each case, the P-R interval was used as the base line from which the RS-T segment depressions were recorded. The RS-T segment depressions were usually more pronounced in leads  $V_4$ ,  $V_5$ , or II than leads I or III.

Eight persons had no significant depressions of the RS-T segments in electrocardiograms following the single "2-Step" test, but did have RS-T depressions of 0.5 mm. to less than 1.0 mm. after the double "2-Step" test (fig. 1). Two individuals had RS-T depressions of

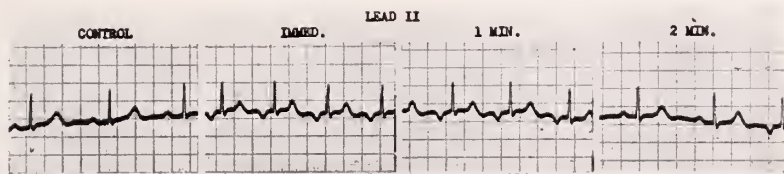


FIG. 2. R. F., 18 year old normal female. Single "2-Step" test. Infrequent auricular premature contractions were present in control record. Note inverted P waves in records taken immediately and one minute after exercise.

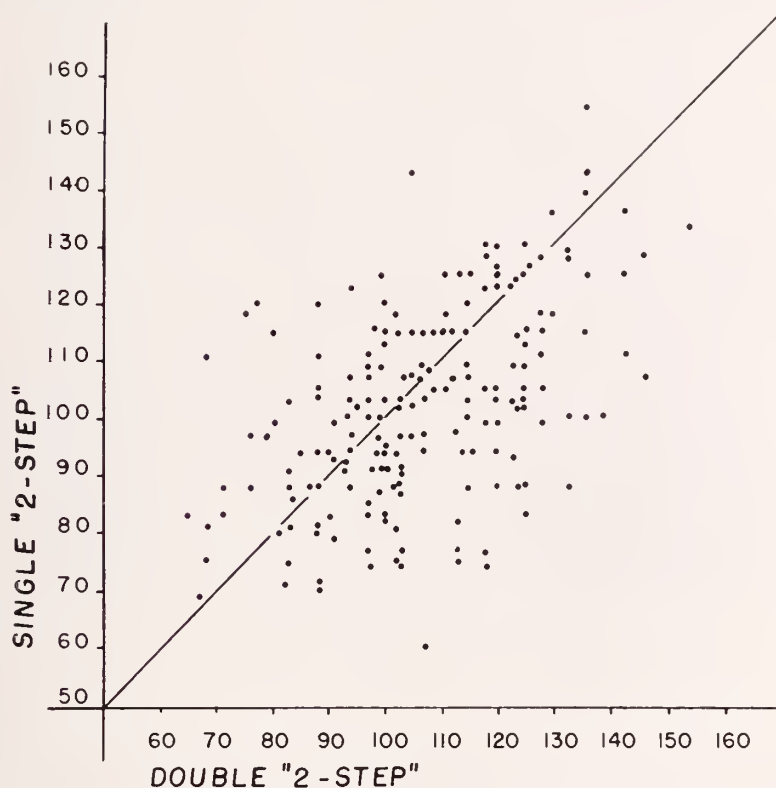


CHART 2. *Absolute Cardiac Rates (negative "2-Step" tests)*: Each point represents one person, and compares the rate immediately after the single "2-Step" test to that immediately after the double "2-Step" test. The points above the 45° line represent those instances in which the absolute cardiac rates were more rapid after the single than after the double "2-Step" test, while those below the line had a more rapid rate after the double.

0.5 mm. to less than 1.0 mm. after both the single and double "2-Step" tests. One person had RS-T depression of 1.5 mm. after the single "2-Step" exercise test, and between 0.5 and 1.0 mm. after the double "2-Step" exercise test. Two persons showed no significant RS-T depression after the double "2-Step" exercise test, but did have a depression of 0.5 to 1.0 mm. after the single "2-Step" test.

None of the changes persisted after the two minute electrocardiogram following the completion of the exercise test. In seven of these tests, all RS-T depressions had disappeared after the recording of the electrocardiograms taken one minute following exercise. Five individuals had RS-T segment depressions present only in the electrocardiograms recorded immediately after exercise. In no instance did the RS-T segment become elevated after exercise.

2. *T Wave Changes.* In no instance did the T wave become inverted in leads I, II,  $V_4$ , or  $V_5$  following exercise. There were numerous instances of minimal alterations in the height of the T waves and these were as frequent amongst those instances of associated RS-T segment depressions as amongst those without such alterations. The T wave became flat

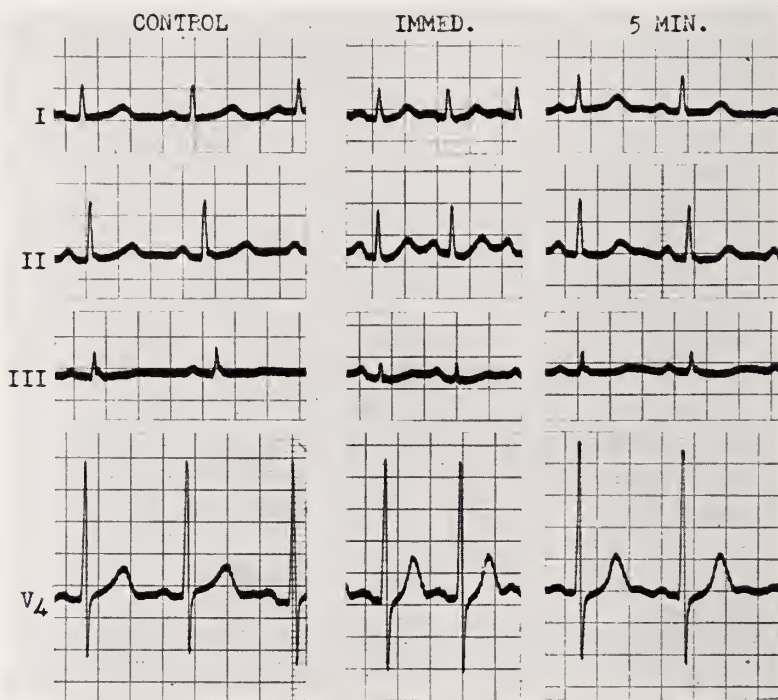


FIG. 3. C. F., 23 year old normal female. Single "2-Step" test. RS-T segment isoelectric despite tachycardia. Note P wave beginning on downstroke of T wave in lead II, immediate record, illustrating the necessity for employing the P R interval as the base line.

after being upright in the resting records in two persons with associated RS-T segment depressions. These latter alterations were present in leads I or II. In one instance the T wave in  $V_4$  became diphasic (plus-minus) immediately following the double "2-Step" exercise test in a patient with associated RS-T segment depression.

The T waves in several instances became of increased amplitude following exercise, these changes usually being seen in  $V_4$  or  $V_5$  in the electrocardiograms recorded immediately after exercise, and less frequently in leads I or II. These changes occurred as frequently in tests with associated RS-T segment alterations as amongst those without such alterations. In four instances, the T waves became flat in II,  $V_4$ , or  $V_5$  immediately after either the single or double "2-Step" test without associated RS-T segment depression. In one instance, the T wave in  $V_4$  became diphasic (plus-minus) immediately after the double "2-Step" exercise test without associated RS-T segment depression.

Lead III showed a wide range in the direction and amplitude of the T wave.

3. *P Wave and P-R Interval.* In a few instances, the P waves became of increased amplitude in leads I and II after exercise. No other significant change was noted. The P-R interval was essentially unaltered after the exercise tests.

4. *QRS Complex.* In no instance did the QRS complex increase or decrease appreciably in duration after exercise. Minor variations in the amplitude of the QRS complex were occasionally seen. No Q waves were observed after exercise which were absent prior to the performance of the tests.

5. *Arrhythmias.* An ectopic auricular rhythm developed in one patient immediately after exercise and persisted for about two minutes. The resting record had revealed only an infrequent auricular premature contraction (fig. 2). Occasional auricular premature contrac-

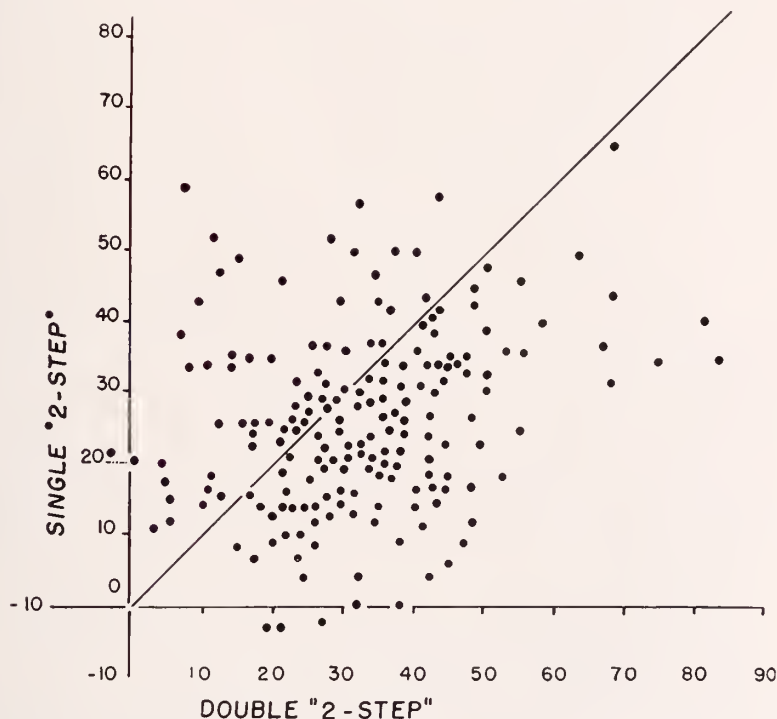


CHART 3. *Change in Rate (negative "2-Step" tests):* Each point represents one person and compares the increment in rate after the single to the increment immediately after the double "2-Step" test.

tions were recorded in three persons after exercise. Ventricular premature contractions rarely occurred. Marked sinus arrhythmia occurred in several patients and was usually more marked in the electrocardiogram recorded one to two minutes after exercise than in the electrocardiogram recorded immediately following the test.

6. *Cardiac Rate.* A. In Chart 2 are plotted the relationships of the *absolute cardiac rates* immediately after the single "2-Step" exercise test to the rates immediately after the double "2-Step" exercise test for the 187 persons (374 tests) without associated RS-T segment depressions. In ten persons the rate became 130 or more following the single "2-Step" test; and in the double "2-Step" test, 19 persons had a rate of 130 or more per minute. In no instance did the rate exceed 154 per minute. The points recorded above the 45° line represent those instances in which the absolute cardiac rate was higher after the single "2-Step" test than after the double "2-Step" exercise



test to produce a more rapid absolute rate than the single "2-Step" exercise test. Despite these rapid rates, no RS-T segment depression was present in most of the cases (fig. 3).

B. The relationship of the *change in rate* produced after the single and double "2-Step" exercise test is plotted in Chart 3 for those individuals without associated RS-T segment depression. Above the 45° line are represented those instances when the change in rate was more following the single "2-Step" test than after the double "2-Step" test, while those below the line represent more rapid rates after the double "2-Step" test than after the single. In ten persons the rate increased by 50 or more after the single "2-Step" test, and in

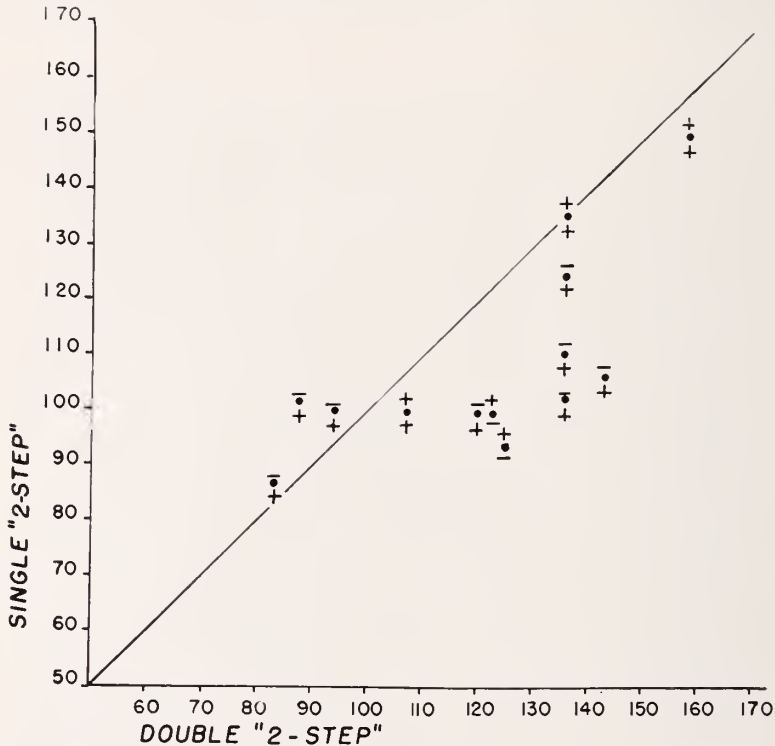


CHART 4. *Absolute Cardiac Rates (positive "2-Step" tests):* Each point represents one person and compares the rate immediately after the single "2-Step" test to the rate immediately after the double. The sign above each point reveals whether there was RS-T segment depression in the single "2-Step" test (+ indicates positive test) while the sign below reveals the same information relative to the double "2-Step" test.

18 persons the rate increased by 50 or more after the double "2-Step". Two individuals had rate increases of over 80 per minute after the double "2-Step" test without associated RS-T changes. The definite tendency for the double "2-Step" test to produce a more marked rate increase immediately following exercise is graphically shown.

In those persons without RS-T changes, within five minutes after exercise, the cardiac rate returned to within 15 beats of the control except in thirty persons; to within 20 beats except for 18 persons; and within thirty beats for all but one person. After the double "2-Step" test, the rate after five minutes was usually higher as compared with the control than after the single "2-Step" test.

C. In Chart 4 are plotted the *absolute cardiac rates* immediately after the single and double "2-Step" exercise tests for those thirteen persons with RS-T segment depressions of more than 0.5 mm. The sign above each point reveals whether there was RS-T depression present

in the single "2-Step" test (+ indicates RS-T depression) while the sign below reveals the same information relevant to the double "2-Step" test. RS-T depressions were associated with cardiac rates of 130 or more in six persons following the double "2-Step" test and in two persons after the single "2-Step" test. RS-T segment depressions of more than 0.5 mm. were present in three persons at a cardiac rate slightly slower after the double "2-Step" test than after the single "2-Step" test. More rapid cardiac rates after the double "2-Step" test in two persons failed to produce significant RS-T segment depressions although slower rates after the single "2-Step" test had produced RS-T segment depressions.

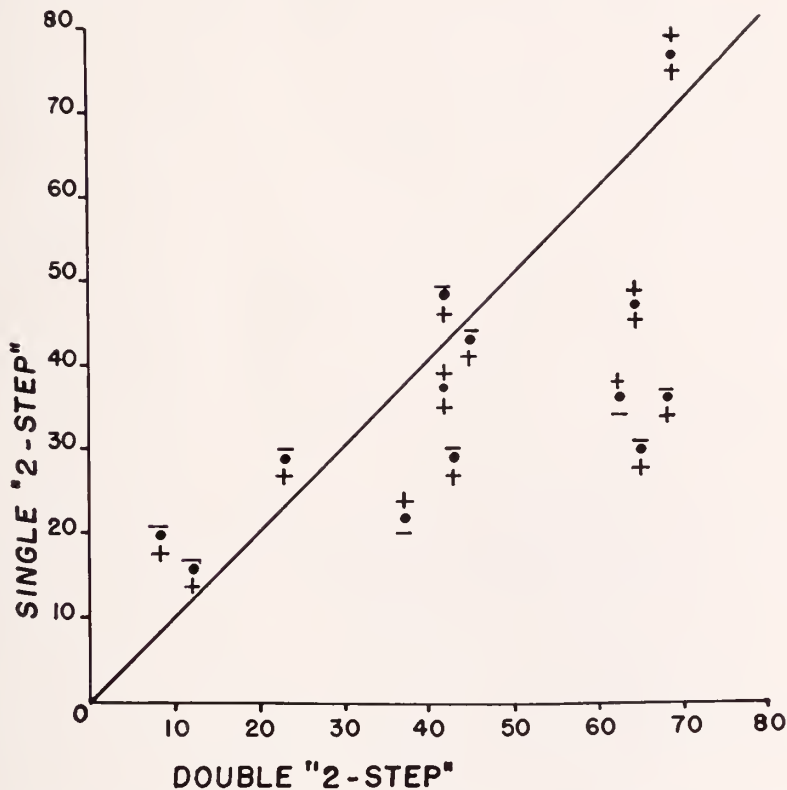


CHART 5. *Change in Rate (positive "2-Step" tests)*: Each point represents one person and compares the increment in rate immediately after the single to the increment in rate immediately after the double "2-Step" test. Symbols are similar to those employed in Chart 4.

D. For those thirteen persons with RS-T segment depressions after exercise, the *change in rate* produced after the single "2-Step" test is plotted against the change in rate after the double "2-Step" test in Chart 5. A rate increase of fifty or more was present in only one person after the single "2-Step" test and in four after the double "2-Step" test with associated RS-T depressions. Rate increases were usually more marked after the double "2-Step" exercise test. In two persons, a greater change in rate after the double "2-Step" exercise test was associated with no significant depression of the RS-T segment while lesser changes in rate after the single "2-Step" test had been associated with RS-T segment depressions of more than 0.5 mm. Within five minutes after exercise, the cardiac rate had returned to within fifteen beats of normal in all but seven of the thirteen persons; to within twenty beats in five; and within thirty beats in all but one.

It is interesting to note that of the sixteen exercise tests with RS-T depressions of more

than 0.5 mm. recorded in the present series, five were associated with an increment of sixty or more in the heart rate of the record taken immediately after exercise as compared to the resting record. However, of the 384 total negative tests, only nine were associated with an increment of sixty or more. Eight of the tests with RS-T depressions of more than 0.5 mm. were associated with an absolute rate of 130 or more in the immediate records, while 29 of the 384 total negative tests had rates of 130 or more.

#### DISCUSSION

The electrocardiogram after standard exercise has been studied in 200 normal persons in relationship to RS-T segment deviation, P and T wave changes, arrhythmias and rate. The effects of standard exercise upon the Q-T interval will be reported separately. Although several other electrocardiographic studies have been made on persons after exercise (5, 6, 7, 8, 9), few studies have employed a standard amount of exercise (10, 11) such as that used in the present investigation, wherein a definite amount of work standardized to the patient's age, sex, and weight is utilized.

Results at variance with the present study have been found when a precordial lead is not utilized. The use of a precordial electrode in the study of RS-T segment changes is of extreme importance since this electrode in the  $V_4$  or  $V_5$  position will be closest to the left ventricle where these changes are most likely to be recorded. It has already been reported that the number of cases showing RS-T segment alterations after exercise is thus increased by the use of a precordial lead (2, 3, 5, 12). In the present study, lead  $V_4$  or  $V_5$  was the lead which most frequently recorded RS-T segment depressions.

The employment of the Wilson unipolar precordial lead is to be preferred since the effect of potentials contributed from areas more remote from the electrode are minimized. It is to be anticipated that a CF lead would show a smaller percentage of RS-T segment changes since any negativity recorded in the precordial lead in such instances would be offset by negativity recorded in the left leg. A CR lead, however, would reveal the additive effects of the RS-T negativity in the precordial lead and whatever RS-T positivity might be recorded in the right arm, both deviations being summated to increase the negative RS-T deflection in the CR lead. It is for the latter reason, apparently, that lead II shows such frequent occurrences of RS-T segment depression, since the negativity of the RS-T depression of the left leg is increased by the positivity of the RS-T segment elevation of the right arm to give increased depression in lead II, which is the resultant of the left leg potentials minus the right arm potentials.

The positivity of the RS-T segment in coronary insufficiency in the right arm is probably due to the fact that in many cases, aVR reflects essentially left ventricular cavity potentials (13). It has been shown that in induced coronary insufficiency, the RS-T segment depression in left precordial leads is associated with RS-T segment elevation in esophageal leads reflecting left ventricular cavity potentials (14).

Prior to the performance of the Master "2-step" exercise test, the standard leads, aVR, aVL, and aVF, and 6 precordial leads are recorded. The test is not routinely performed unless the resting record is normal. The precordial lead

employed after exercise in this study has usually been  $V_4$ . However, the  $V_5$  position was frequently used in those instances when a prominent S wave was present in  $V_4$ . In the presence of such a deflection, the determination of the degree of RS-T segment depression can be extremely difficult. The preferable position is  $V_4$  or  $V_5$ , whichever shows the best combination of an R wave of high amplitude and an S wave of minimal amplitude.

When the effect of exercise upon the electrocardiogram is to be recorded, it is essential that the records be obtained promptly after exercise (5, 6). It is for this reason that all of the electrodes are maintained in position throughout the performance of the test, and that an electrocardiograph of the amplifier type with instomatic control is employed. Such an instrument permits the recording of leads I, II, III and  $V_4$  within 20-35 seconds after the completion of exercise. It is to be expected that with the longer periods of time elapsing when other instruments are used, fewer RS-T segment depressions will be recorded since, in several instances, the deviations are no longer present after one minute although still present immediately after exercise. Rapid rates present in the immediate record frequently subside within the period required to record I, II, III and  $V_4$  utilizing other types of cardiographs.

The results of the present study are of practical importance in that such standard exercise tests are utilized to determine cardiac function, especially in regard to coronary insufficiency. It is a well known fact that many individuals with coronary disease and a typical history of angina pectoris have normal resting electrocardiograms. Only with increased work of the heart are changes provoked in the electrocardiogram of such individuals. The increased amount of work as entailed in the double "2-step" exercise test has been advocated in those cases where the single "2-step" test fails to provoke electrocardiographic changes (1, 2, 3).

The criteria for a positive single or double "2-step" exercise test are as follows (the presence of one provides evidence of coronary insufficiency): 1) using the P-R interval of the electrocardiogram as the control or isoelectric level, depression greater than 0.5 mm. of the RS-T segment below this level in any lead. 2) A change from an upright T-wave to an isoelectric (flat) or inverted T-wave, or a change from a negative to a positive T-wave (with the exception of lead III). 3) Premature beats or more significant arrhythmias, widening of the QRS, large Q waves, prolongation of the P-R interval, and heart block.

Of the 200 normal persons included in the present report, 187 failed to show a depression of the RS-T segment greater than 0.5 mm. in any lead after either the single or double "2-step" exercise test. Four persons had depressions of the RS-T segment of more than 0.5 and less than 1.0 mm. after the single "2-step" exercise test while one had a depression of 1.5 mm. after this test. Eleven individuals had depressions of the RS-T segment of more than 0.5 and less than 1.0 mm. after the double "2-step" exercise test. Of this latter group, three also had similar depressions after the single "2-step" test. Thus, on the basis of the criteria pertaining to the RS-T segment depression, 2.5 per cent of the 200 normal persons studied had positive single "2-step" tests, 5.5 per cent had positive double



"2-step" tests, and 6.5 per cent had either positive single or double "2-step" tests or both. In four persons without associated RS-T segment depression, the T wave became flat immediately after exercise. There was no instance of inversion of the T wave in any instance in lead I, II, or  $V_4$  following exercise. Flattening or inversion of T waves have also been infrequent in similar studies using the Master "2-step" exercise test as reported by others (10, 11). Increased amplitude of the P wave, as obtained in this study, was seen with high frequency in a study by others (15).

There was a definite tendency in the present study for the tests with more rapid absolute rates and greater increments in rate to be associated with depressions of the RS-T segment more than 0.5 mm. in the 200 normal persons included in the present report.

Further work is being carried on in a larger group in an attempt to evaluate additional effects of standard exercise upon the electrocardiogram, including the Q-T interval.

#### SUMMARY

Two hundred normal individuals performed the Master single and double "2-step" exercise test. On the basis of RS-T segment depression, 2.5 per cent had positive single "2-step" tests, 5.5 per cent had positive double "2-step" tests, and 6.5 per cent had either positive single or double "2-step" tests or both. The effects of the single and double "2-step tests" upon the absolute cardiac rates and increments in cardiac rate are reported for both the negative and positive tests.

We wish to express our appreciation to Mrs. Steven Ogden, Miss Edith G. Stern, Miss Janice Newman, Miss Ann Coleman, and Miss Nancy Miller for technical assistance.

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# AMYLOID DISEASE OF THE URINARY BLADDER

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Amyloid disease is uncommon, but the occurrence of a localized deposit of this substance within an organ is most unusual. A review of the literature discloses the presence of nine instances wherein the urinary bladder was involved with amyloid. The characteristic symptom in all cases was that of hematuria. In some, the gross appearance of the lesion strongly resembled that of a malignant neoplasm. The case report which follows evidenced profuse vesical bleeding and the diagnosis was made by an alert pathologist from a chance cystoscopic biopsy.

## CASE REPORT

*History.* S. K., aged 53 years, married woman, was first seen on July 9, 1948. Her only complaint was the sudden onset that morning of profuse, gross and painless hematuria. Some dysuria was associated with the passage of clots. The urinary bleeding apparently was initiated by the straining incidental to the act of defecation. Other than this her general health had been good except for chronic constipation.

*Examination.* The patient was a rather thin individual. The head showed no abnormalities. The eye grounds, tongue and pharynx were normal. The neck failed to disclose any thyroid or lymph node enlargement. The heart and lungs were normal to percussion and auscultation. Examination of the abdomen revealed no evidence of any masses. The liver, spleen and kidneys were not enlarged nor palpable. There was a reducible right femoral hernia. Pelvic examination was normal. Catheterization of the bladder yielded a grossly bloody urine with numerous clots. A 21 French Brown-Buerger cystoscope was introduced into the bladder and all the clots were evacuated. Inspection of the bladder revealed a slightly injected mucosa with normal ureteral orifices. Well behind the right ureteral orifice and on the postero-lateral aspect of the bladder floor, a bleeding area was found which seemed to arise from a dilated vein. Hemostasis was accomplished by electro-coagulation.

*Course.* July 12, 1948: There has been no urinary bleeding. A flat Roentgen film of the abdomen failed to show any abnormality in the size, shape or position of the kidneys. There were no opaque urinary calculi. Intravenous urography using 20 cubic centimeters of 50 per cent neo-iopax showed both kidneys to be grossly normal. The bladder was regular in outline and was without filling defects.

November 30, 1948: The patient had a recurrence of gross hematuria including the passage of clots. During my absence, cystoscopy was carried out by Dr. Stanley Glickman who reported as follows: "The bloody urine and blood clots were evacuated. The bladder was normal except for some adherent blood clots just above the right ureteral orifice. After removing these clots a small area of reddish mucosa was exposed which was slightly elevated, and from its center a constant oozing of blood was controlled by fulguration."

March 3, 1949: The patient has been having some frequency of urination. A catheterized bladder urine specimen was clear and normal except for a small number of pus cells. Cystoscopic examination was done. This showed numerous dilated blood vessels throughout the mucosa. On the right side of the bladder and at about 7 o'clock, there appeared to be a localized bulging underneath an intact mucous membrane. The mucosa proper was normal in appearance and slightly yellowish in tint. It must be emphasized that no real lesion was found to account for the attacks of hematuria. Biopsy specimens were taken from the slightly bulging area in order to exclude a submucosal infiltrating malignant lesion. Profuse bleeding resulted from the biopsied areas, necessitating electro-coagulation to arrest the oozing of blood. One of the striking features noted was the difficulty with which the bleeding

areas responded to electro-coagulation as compared with the usual effectiveness in bleeding from bladder tumors.

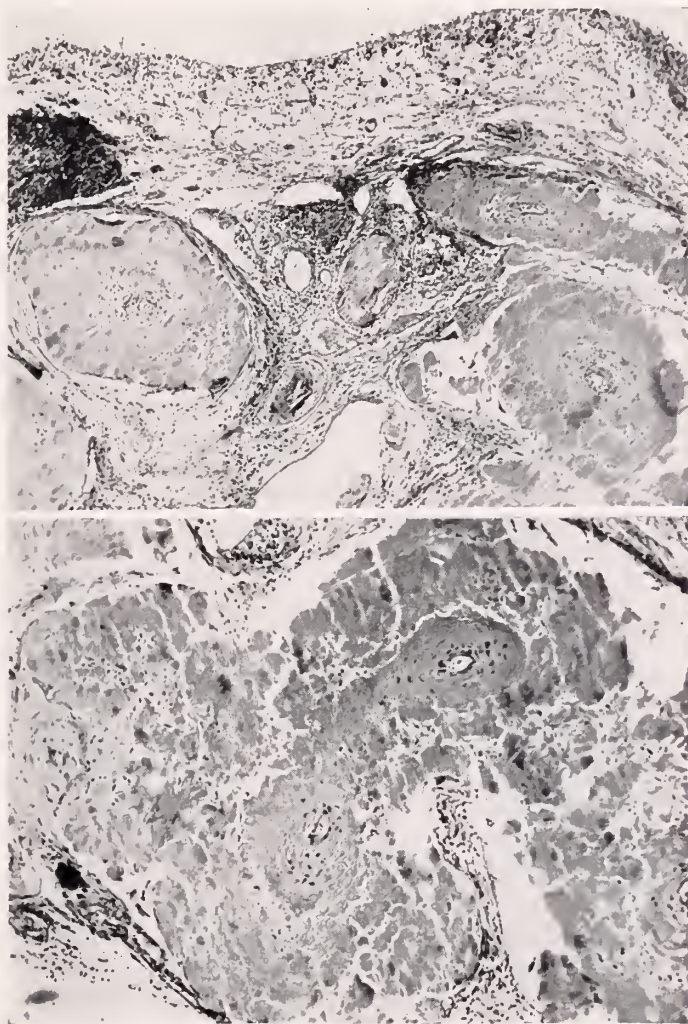


FIG. 1. Histologic character of the lesion: A, section including epithelial lining; B, section of deeper area.

The biopsy specimens were examined by Dr. Joseph C. Ehrlich who reported the following:

*"Gross Description:* There are several fragments of friable gray tissue received in fixative.

*"Microscopic Findings:* The sections reveal fragments of tissue from the urinary bladder. In a few areas the transitional epithelium is present on the surface but most of the specimen represents the deeper tissue of the bladder wall. The specimen is characterized by the presence of round and oval nodules composed of homogeneous eosinophilic material which gives a positive reaction for amyloid. In the center of each nodule a small artery or arteriole is present. Severe secondary chronic inflammatory changes of a non-specific character are



present. There is no histologic evidence of malignancy. Diagnosis: Bladder tissue showing severe chronic inflammation and extensive deposits of amyloid" (fig. 1).

The patient was urged to enter the hospital for more extensive studies but this was declined. She was then referred for blood studies to Dr. Peter Vogel who reported the following:

"Urea nitrogen of the blood, 13.8 mg. per cent; cephalin flocculation test, negative, the immediate direct Van den Bergh reaction, negative; the delayed reaction, weakly positive; the icteric index, 11.8; and the blood count, essentially normal.

A Congo Red test was contemplated but could not be carried out because the drug had been withdrawn from the market by the federal government because of some severe untoward reactions.

*August 12, 1949:* The patient voided a slightly bloody urine. Cystoscopic examination showed no change from that described March 3, 1949. The bleeding ceased spontaneously.

She was next seen on September 22, 1949 at which time her catheterized urine was entirely normal.

*December 5, 1949:* Hematuria recurred. General physical examination was negative. Cystoscopy revealed a marked swelling of the right ureter area and of the tissue behind it. Several specimens were removed for biopsy from this region. This area was approximately 3 to 4 cm. from the site of original biopsy. This was followed by profuse bleeding which required fulguration. The following day the bleeding recurred and again cystoscopy and electro-coagulation had to be carried out.

The tissue removed was examined by Dr. Joseph C. Ehrlich who again reported the presence of amyloid deposit in the bladder tissue.

The patient has not been seen since December 12, 1949.

#### DISCUSSION

Amyloid disease is normally considered under four headings: 1) primary, 2) secondary, 3) that associated with multiple myeloma, and 4) that which is limited to a single location.

Primary systemic amyloidosis is rare. Prior to 1946, only 46 cases of this type had been reported in the literature and in only eight of these was the diagnosis made before necropsy as a result of a biopsy. It is characterized by the following features:

1) The deposits of amyloid are chiefly within the skeletal, cardiac and smooth muscles. 2) Slight if any deposition occurs in the organs usually the seat of secondary amyloidosis such as the liver, spleen and kidneys. (3 The deposits tend to be nodular rather than diffuse. 4) Such causative factors as tuberculosis, suppurations etc. are absent. 5) The amyloid has a variable staining reaction.

Cases of primary systemic amyloidosis may live for a long time. The longest survival period thus far has been 14 years. Death is usually from congestive heart failure as a result of myocardial involvement; or from a terminal infection; or from a massive gastro-intestinal hemorrhage.

Secondary amyloidosis is the commonest form of the disease. The organs which are apt to be most involved are the liver, spleen and kidneys. It is usually associated with some chronic disease as tuberculosis or chronic suppuration but other etiologic factors have been described such as rheumatoid arthritis, ulcerative colitis and malignant neoplasms. Once this condition develops the patient rarely survives for more than one year. Death commonly results from either the causative disease, intercurrent infection or progressive renal insufficiency.

Significant cases have been reported in the literature wherein the amyloidosis regressed after removal of a suppurative focus. Some have advocated the use of liver extract. In one case which we previously reported, the removal of a hypernephroma of the kidney and the use of large doses of liver extract failed to prevent the remaining normal kidney from developing a progressive amyloidosis which led to azotemia and death.

The association of amyloidosis with multiple myeloma has been so striking that it has been segregated into a separate class. Here the pinkish substance is deposited especially around the joints and blood vessels.

Isolated and localized aggregates of amyloid material may develop in various structures. These have been described in the larynx, upper respiratory tract, the eye, the tongue and within the genito-urinary tract. This type is not associated with the generalized forms of amyloidosis. These solid deposits may take the form of a tumor and for this reason they have been referred to as amyloid tumor.

Amyloid stains red with congo red and blue with iodine. For many years it was considered to be a chondroitin sulphuric acid compound but this has not been accepted at the present time. It is now believed to be an abnormal protein substance which has not as yet been identified. The relationship of this peculiar substance to the tendency to bleeding has been noted but has not been satisfactorily explained.

The diagnosis of amyloidosis is frequently suspected clinically but can only be confirmed during life by a positive biopsy. The retention by the tissue of 95 per cent or more of congo red dye when injected intravenously is most suggestive of the condition. This is only applicable to the generalized form of the disease.

*Localized Amyloid of the Urinary Tract.* Solitary deposits of amyloid or so-called amyloid tumor have been described in various parts of the urinary tract. Amyloid of the urethra was reported by Tilp (1909); Herxheimer and Reinhart (1913); and by Von Albertini (1925). In Chwalla's case (1932) the lesion was located on the internal sphincter of the bladder classifying it as a urethral as well as a vesical case. In 1927, Akimoto reported a case of localized amyloid tumor of the renal pelvis while in 1927 Lehmann described an instance of a purely localized deposit of amyloid in the wall of the ureter. The male reproductive tract has also been the seat of this peculiar substance.

The urinary bladder has been the site of predilection in the largest number of cases.

The *earliest case* reported was that of Solomin (1897) who found at the autopsy of a 73 year old woman a plaque of amyloid, 8 centimeters in diameter, situated on the posterior wall of the bladder.

The *second case* was that reported by Lucksch (1904) who found at necropsy multiple nodules of amyloid in the bladder of a 42 year old woman who succumbed to pulmonary, laryngeal and intestinal tuberculosis.

A *third case* was reported by Chwalla (1932). This was a 57 year old male in whom two years previously a typical papilloma of the bladder neck was destroyed by electro-coagulation cystoscopically. He was admitted because of a poor urinary stream which led to acute urinary retention. Following catheterization of the bladder hematuria developed. A solid tumor was seen cystoscopically at the site of previous fulguration. This was excised

suprapubically. In the discussion, Chwalla considers the relationship of the previous tissue destruction to the formation of amyloid.

The *fourth case* was reported by Rusehe and Bacon in 1941. This was a 51 year old woman with gross hematuria. Two years previously a "wart" in the bladder had been fulgurated. Cystoscopy revealed an infiltrating tumor on the left side of the bladder. This was removed by a partial bladder resection without a previous bladder biopsy. Nine months later, a cystoscopic biopsy taken from the area adjacent to the site of the lesion was reported as negative for amyloid.

A *fifth case* was recorded by the same authors, in the same year. It was that of a 69 year old male, who had had intermittent hematuria for 25 years but in whom the bleeding had been continuous for the preceding 9 months. Cystoscopic examination disclosed an irregular, hemorrhagic, ulcerated lesion 3 centimeters in diameter. Biopsies taken on 3 different occasions failed to show any evidences of a malignant tumor. A fourth biopsy was stained for amyloid and was found to be positive. A transurethral prostatectomy was subsequently done but the prostatic tissue did not show evidences of amyloid.

A *sixth case* was described by Corbitt, Broders and Pool in 1944. This was a 59 year old woman who complained of gross hematuria. She was found to have a large fungiform type of tumor on the left side of the bladder. Biopsy specimens revealed the presence of amyloid. The Congo Red test was negative. Treatment consisted of a partial cystectomy.

The *seventh case* was published by Purell and Brown in 1946. This was a seaman who was admitted with gross hematuria. Cystoscopic examination showed the presence of a small sessile lesion on the anterior wall of the bladder which was yellowish in color and oozed blood. Because the condition was thought to be a neoplasm, a partial resection of the bladder was performed. The specimen revealed amyloid.

The *eighth case* was reported by Craig in 1949. A 49 year old man was seen because of a sudden onset of massive urinary bleeding which was followed by acute urinary retention. On cystoscopic examination a flat, slightly elevated "infiltrating" tumor was noted on the floor of the bladder. This was yellowish in color, not ulcerated and oozed blood. Biopsy specimen showed the presence of amyloid. The area was treated by electro-coagulation.

The latest and *ninth example* of amyloid disease of the urinary bladder was described by Senger, Thomley and McManus in May 1950. This was a 49 year old woman with hematuria who was found to have a large, irregular, ulcerated mass on the floor of the bladder 6 by 8 cm. in size. It had the gross appearance of a malignant tumor. A partial cystectomy was done and radon seeds were implanted into that part of the tumor which could not be resected. The tumor proved to be amyloid.

The foregoing ten cases disclosed the fact that common to this group and the outstanding symptom was hematuria, which was usually sudden in onset and at times profuse. In each instance except our own, the cystoscopic picture was that of a lesion which closely resembled the gross appearance of an infiltrating bladder neoplasm. Four patients were treated by a partial resection of the bladder while in two cases the lesion was treated transurethrally by electro-coagulation. Because of the poor demarcation of the lesion in our case, specific therapy for its extirpation could not be carried out.

#### SUMMARY

1. A case of so-called solitary amyloid deposit of the urinary bladder was presented; it is the ninth instance recorded in the literature.
2. Hematuria was a common symptom in all of the cases observed clinically.
3. The cystoscopic appearance of the lesion closely resembles that of an infiltrating bladder neoplasm.

4. In no case was the diagnosis made clinically. The true pathologic character of the lesion was established by biopsy.

5. The etiology of this condition is obscure. Treatment thus far has been by either a partial resection of the bladder or electro-coagulation.

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# CARCINOID OF THE DUODENUM\*

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Carcinoids comprise 0.42 per cent of gastro-intestinal tract tumors. They arise anywhere along the intestinal tract, but 90 per cent are most commonly found in the region of the ileo-cecal junction. Rarely are they primary in the stomach, duodenum, and jejunum. Masson (8) has shown that the argentaffin tumors take origin from the Kulchitsky or argentaffin cells found in the bases of the crypts of Lieberkuhn. The function of these cells is obscure, but a neuroendocrine relation is presumed because of the connections with the nerves of Meissner's plexus. The tumor formations may be single or multiple; usually they are sub-mucosal but quickly penetrate the muscularis and serosa. Subsequent pathological complications may be intestinal obstruction by the tumor mass forming the head of an intestinal intussusception, or causing a kinking or knuckling of the intestine.

Opinions vary as to the degree of malignancy of carcinoids (3, 6). The apparent benignity of the appendiceal carcinoids is due to the early production of symptoms and removal before the opportunity for metastases. The larger the tumor, the greater the tendency to metastasize. Aside from direct extension to lymph nodes, metastases have been reported in the liver, spleen, lungs, vagina, and the dura of the spinal cord. The prognosis of argentaffin tumors of the small bowel is good, especially if the symptoms occur early, and a radical resection is performed. Even with lymph node metastases some reported cases lived up to 19 years after operation.

Intestinal carcinoid should be considered in patients with repeated episodes of partial intestinal obstruction. X-ray study of the small bowel should be done, and, if a small filling defect is found with kinking at the site of obstruction, it is to be regarded as of diagnostic significance according to Miller and Herrmann (9). The x-ray sign is based upon the tendency of carcinoids to invade the mesentery and produce knuckling of the bowel at that point. Melena is rarely a symptom as mucosal ulceration is unusual.

Nine cases of carcinoid of the duodenum have been previously reported (1, 2, 5, 11). To this group, the following case is added.

## CASE REPORT

*History:* J. L., a white man aged 65 years was admitted to The Mount Sinai Hospital on May 25, 1950 complaining of epigastric pain and melena for the past three years. The patient has been a known diabetic for the past eight years, controlled by diet alone. He was well until three years ago at which time he developed pain over the precordium and epigastrium, dull in nature, radiating down to the umbilicus, unrelated to meals, worse at night, and relieved only by alkalis. Twenty-five years ago, the patient had a rectal procedure performed, and a subsequent stricture developed. Two and a half years ago, a rectal plastic operation was performed, with good results, and the patient noted relief of his epi-

\* From the Surgical Service of Dr. John H. Garlock The Mount Sinai Hospital, New York.

gastric distress. However, about three weeks ago, symptoms recurred with several episodes of melena. A medical work-up, including a gall bladder series, electrocardiogram, barium enema, and gastrointestinal series was carried out. The gastrointestinal series was reported as showing several polypi in the duodenum (fig. 1). Systemic review was negative.

*Examination:* The abdomen showed a thick panniculus with diastasis recti in the epigastrium. There were no areas of tenderness; no palpable masses and no herniae. There



FIG. 1. Roentgenogram; showing in the first portion of the duodenum two areas of apparent filling defects are seen. Arrow indicates defect in duodenal wall found at operation with the mucosal pattern of duodenum well outlined.

was a good rectal sphincter tone, and an adequate outlet. The prostate was normal, and no masses were palpable on rectal examination. There were bilateral varicose veins with no edema of the lower extremities. There were multiple papillomata of the skin.

*Laboratory data:* Blood urea nitrogen, 16 mg. per cent. Fasting blood sugar, 160 mg. per cent. Hemoglobin, 14.7 Gm. White blood count, 6,200: 69% segs., 2% nonsegs., 19% lymphs, 10% monocytes. The urine showed a trace of sugar; no acetone.

*Course:* A preoperative diagnosis of polypi of the duodenum with melena was made, and

on May 29, 1950, the patient was explored through an upper abdominal midline incision (Dr. Garlock). A very fat and heavy gastro-colic omentum was found with a short, fat infiltrated transverse mesocolon. The liver was shrunken in size, finely granular with a rounded and irregular edge and a cobblestone surface. The spleen was normal in size. The veins were moderately dilated. All tissues were very friable and bled readily suggesting a portal hypertension. The stomach was apparently normal. There was some scarring and thickening of the pre-pyloric region, the pylorus, and the first portion of the duodenum; the second and third portions of the duodenum were normal. The entire small bowel was explored and found to be normal. A subtotal gastrectomy (Hofmeister retrocolic gastro-enterostomy) was performed. Within the first 24 hours after operation, approximately 2,000 cc. of venous blood and clot were aspirated from the Levin tube. The blood was replaced and the patient received 11 units of whole blood in that period of time. The blood pressure returned to normal, 140/80. A blood examination showed: hemoglobin, 12.6 Gm., red blood count, 4.4 million; and hematocrit, 42.5%. The oozing occurred from the suture

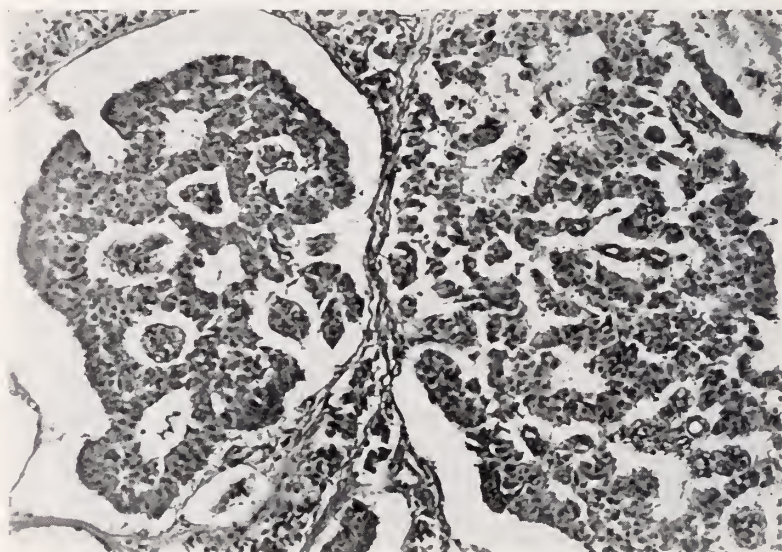


FIG. 2. Microscopic appearance of the duodenal carcinoid

line and was probably due to the portal hypertension secondary to the cirrhotic liver. The remainder of the postoperative course was uneventful. The patient was treated with the usual postgastrectomy regime. The wound healed; clips and drains were removed on the eighth postoperative day, and the patient was discharged from the hospital on June 12, 1950.

*Pathology report:* (P 48639) Specimen consists of a subtotally resected stomach, which measures 7 cms. along the proximal line of resection,  $8\frac{1}{2}$  cms. along the lesser curvature and 15 cms. along the greater curvature. About  $1\frac{1}{2}$  cms. of the duodenum are present beyond the pyloric ring. Arising from the duodenal aspect of the pyloric ring, there is a firm, elevated nodule, measuring about 5 mm. in diameter and raised from the surface to a height about  $2\frac{1}{2}$  mm. This nodule is covered with mucosa and is quite discrete. Underlying it there is no area of serosal scarring. Remainder of the duodenum reveals a pseudo-diverticulum about  $\frac{1}{2}$  cm. distance from the nodule described. Diagnosis: Carcinoid of the duodenum and pseudo-diverticulum of the duodenum.

The histologic appearance of the lesion is illustrated in Figure 2, which shows the characteristic hyperchromatic nuclei within the cells arranged in a pseudoglandular fashion. Under higher magnification, the cells exhibited basal cytoplasmic eosinophilic granules,

which are argentaphilic in character. Vascularity is not prominent, and mitoses are not frequent.

#### COMMENT

This patient had a healed duodenal ulcer to account for his bleeding. The carcinoid is not considered to be the cause of the bleeding but merely an incidental surgical finding. None of the reported cases had been diagnosed clinically; they were discovered either during the operation or at postmortem examination. Reviewing the x-rays, the arrow (fig. 1) demonstrates the nodular submucosal duodenal carcinoid.

#### SUMMARY

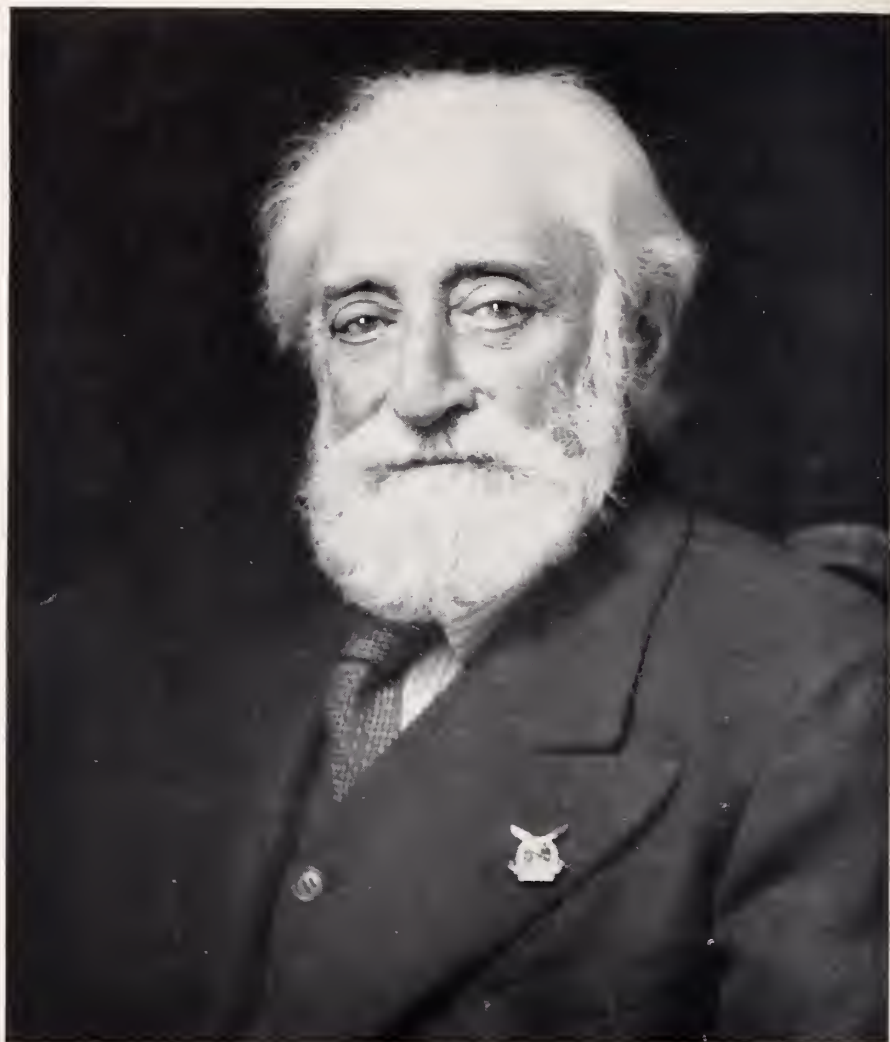
A case of carcinoid of the duodenum is presented as an incidental finding and the salient features of intestinal carcinoid are described.

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Alfred Meyer, M. D.

## Alfred Meyer, M.D.

1854-1950

When on July 14, 1950, Dr. Alfred Meyer died in his 97th year, at his summer home in Maine, probably the last of the outstanding medical figures of the 19th Century passed on. He was born on June 18, 1854, in Amos Street, New York City. Though he left Greenwich Village in his early youth, during his entire lifetime he considered himself a "Villager".

He was educated at Columbia College and the College of Physicians and Surgeons, Columbia University. He received his M.D. degree in 1877. At the time of his death he was the oldest living graduate of the College. Following an internship at the Mount Sinai Hospital, he studied abroad in Vienna and Leipzig. During his active medical career, he was closely associated with the Mount Sinai and Montefiore Hospitals, and served as Clinical Professor at New York University and Bellevue Medical College.

To Dr. Meyer, his hospital service was not just a matter of routine rounds and care of the sick. He was at all times actively interested in the improvement of the hospital in its relation to the patient, the interne staff, and the community. "Actively interested" to him meant personal service in promoting improvements. It was he who proposed the establishment of a house staff library, and he headed the list of subscribers to the fund that he collected.

As a teacher, he stressed the value of attention to detail in arriving at a diagnosis, or in the judgement of the progress of a case. It was his keen observation of minutiae, combined with an ability to demonstrate slight deviations from the normal physical signs, combined with an unusually good memory for recalling similar cases, that made him so outstanding in diagnosis, and sought after as a consultant.

He manifested an especial interest in pulmonary diseases, and achieved recognition as an authority in that field. In 1889 he was appointed the visiting physician to Bedford, the Country Sanatorium for Tuberculosis, of the Montefiore Home, which position he filled until his retirement in 1919. It is in the field of Tuberculosis that Dr. Meyer left an everlasting imprint. He was one of the early advocates of the use of artificial pneumothorax for collapse of the diseased lung. He was one of the founders of the National Tuberculosis Association. He served as a director from 1906 to 1921, and as vice president from 1918 to 1919. He was made an honorary member in 1923. He was a director of the New York Tuberculosis Association from its incorporation in 1919 until his death. He was one of the prime movers in arranging for the International Congress of Tuberculosis in Washington in 1908. He took an active part in the establishment of the New York State Sanatorium at Ray Brook in 1904, of the New York City Sanatorium at Otisville in 1906, and the Bedford Sanatorium. Apropos of this communal work in the field of tuberculosis, Dr. Burns Amberson, in 1942, in awarding him a testimonial for the New York Tuberculosis Association stated, "It may, therefore, be said that the work and influence of Dr. Meyer in this field

has covered half a century, during which the impact of his energy, his courage, and his zeal for the prevention and control of tuberculosis has been felt, not only in our own city but in this state, throughout the nation, and indeed, throughout the world". This was not extravagant praise but was an appreciation of the tremendous expenditure of energy by Dr. Meyer (up to the breaking point), in travel—in interviews—in conferences and in meetings, to promote the various educational and building projects in the control of tuberculosis.

From his devotion to, and his tireless efforts in, the promotion of civic projects, much may be learned of Dr. Meyer's personality and character. He was a man of vision, with progressive ideas. He showed this, not only in his own work for the care of and the control of tuberculosis, but in his broad outlook on education. He gave of himself, his time and his money, in backing the efforts of his wife, Annie Nathan Meyer, in the founding of Barnard College. He was a tireless worker and a courageous fighter, always on the side of the truth. With the whole truth there was never any compromise. He paid incredible attention to details and had, until well along in his nineties, a memory that stored and could recall them at will.

In contrast to these attributes of strength, he had a simple sweetness of character, an appreciation of, and tolerance for, the point of view of others, and a keen sense of humor. He was sympathetic, as shown not only in the sick room but in his quick and generous response to appeals for charity. He was an outstanding musician who, in spite of a busy medical career, found time to maintain his skill at the piano by daily practice. In spite of his frail build, (he was often called "the little doctor"), he was an outdoor enthusiast, a good hunter, fisherman and walker. Without exception, people were attracted to Dr. Meyer at their first meeting. This was not a result of his "turning on the charm", for day after day and year after year, the same attraction was ever present, as there was ever present the ability to discuss music, art, literature, botany, sports or medicine.

He lived 25 years after he had retired from active practice, but he did not stagnate. His medical readings continued to the end, as did his reading of biographies and current events.

Himself—but only himself—he ruled, body and mind, with a rigid discipline. His attitude to the rest of the world was one of friendly leniency and a constant readiness to serve.

## ABSTRACTS

### AUTHORS' ABSTRACTS OF PAPERS PUBLISHED ELSEWHERE BY MEMBERS OF THE MOUNT SINAI HOSPITAL STAFF

Members of the hospital staff and the out patient department of the Mount Sinai Hospital are invited to submit for publication in this column brief abstracts of their articles appearing in other journals.

*Aseptic Necrosis in Gaucher's Disease.* ALVIN M. ARKIN AND ALBERT J. SCHEIN. J. Bone & Joint Surg., 30-A: 631, July, 1948.

Six cases were presented to illustrate the point that aseptic necrosis, secondary to Gaucher's Disease, can cause bone changes indistinguishable from those occurring in aseptic necrosis due to any other condition. Gaucher's Disease causes changes in the adolescent femoral head, similar to those seen in idiopathic aseptic necrosis. The changes in the long bones resemble those seen in Caisson's Disease. The changes in the femoral head are reversible and the value of bed rest during the period of reconstitution of the head is emphasized.

*Granuloblastoma, a Primary Neuroectodermal Tumor of the Cerebellum.* J. EPSTEIN AND A. SACCONI. J. Neuropath. and Exper. Neurol., 7: 287, July, 1948.

Two cases of primary neoplasm of the cerebellar hemispheres in males of 12 and 18 years of age are described. In structure and cellular derivation, they bear a striking resemblance to the granuloblastomas defined by Stevenson and Echlin. The tumor cells in their appearance and migratory behavior recapitulate many phases in the embryonal and early post-natal development of the cells of the granular layer in the cerebellum. The persistent external granular layer in these cases may be considered as a possible anlage from which the neoplasm arose. The presence of both spongioblastic and neuroblastic elements in these tumors is evidence of the bipotential character of the wandering neuroepithelial cells of the external granular layer of the cerebellum. By invading the molecular layer and the underlying structures and by extending inwards from the altered, persistent external granular layer the tumor cells recapitulate the formation of the granule cell layers of the cerebellum. The pattern of growth and the cytological features of this neoplasm are sufficient to warrant their being considered as a special form of primary neuroectodermal tumor of the cerebellum.

*Postganglionic Site of Action of Nicotine with Special Reference to its Direct Action on Blood Vessels.* HENRY HAIMOVICI. Proc. Soc. Exp. Biol. and Med., 68: 516, July, 1948.

In an isolated vascular bed, such as the Laewen-Trendelenburg preparation in the frog, nicotine induces marked vasoconstriction. Resection of both sympathetic chains and of all spinal nerves does not alter the action of nicotine. Tetraethylammonium ion, capable of blocking the action of the "nicotinic-stimulating" substances upon ganglion cells, curare, capable of paralyzing postganglionic fibers, and Dibenzamine, capable of blocking the same fibers, do not abolish the vasoconstrictor action of nicotine. Serial sections of the vessels of the frog's hind legs have shown the absence of ganglion cells. It appears, therefore, that in the Laewen-Trendelenburg preparation the site of action of nicotine is peripheral to the postganglionic fibers, possibly directly on the blood vessels. In the intact animal, it may be assumed that in addition to its known sites of action on ganglion cells, and adrenal medulla, nicotine may also act directly on the neuroeffector cells of the blood vessels.

*Intracranial Novocain Anesthesia in Frogs.* B. KISCH. Am. J. Physiol., 154: 80, July, 1948.

A method is described for immobilizing and anesthetizing frogs by intracranial injection



of approximately 0.5 cc. of a 3 to 5 per cent solution of novocain. The anesthesia which follows a short stage of excitation lasts about 1 hour. It is followed by complete recovery. During the anesthesia the behavior of the reflexes and the influence of the position of the animal on leg reflexes and croak reflexes were studied. During the time of recovery a kind of nystagmus equivalent appeared spontaneously, or it could be provoked as a reflex by touching the eyeball or the belly.

*Photosensitization Therapy of Acne Vulgaris.* A. KURTIN AND R. YONTOF. New York State J. Med., 48: 1606, July, 1948.

Inasmuch as sunlight benefits the skin in acne patients, an ointment was created which would deliberately photosensitize the skin in the treatment of acne. All cases of acne were cleared in a sixteen week period. The formula follows: Crude coal tar 5%, Sulfathiazole 5%, Sulphur ppt. 5%, Lanolin and Lassar's paste, equal parts q.s. No cases of intolerance to this medication was found in a series of several hundred patients.

*Rectal Polyps Showing Early Malignant Transformation.* H. PESKIN. New York State J. Med., 48: 1599, July, 1948.

In this paper 3 cases of rectal polyp are reported, each showing early malignant transformation. In 2 of the cases the first biopsies were reported as benign but later biopsy taken during the course of fulguration revealed carcinomatous degeneration. In the 3d instance the original biopsy is reported as "adeno-carcinoma of infiltrating tendency" but after removal of the polyp surgically, the remainder, as well as the pedicle, revealed no evidence of malignancy. A discussion of the significance and the importance of early examination, careful biopsy, and choice of treatment completes the article.

*Fluorophotometric Method for the Estimation of Salicylate in Blood.* A. SALTZMAN. J. Biol. Chem., 174: 399, July, 1948.

Solutions of salicylate fluoresce a bright bluish violet under ultraviolet light. The fluorescence is intensified by addition of alkali. A simple procedure for direct determination of salicylates in tungstic acid blood filtrates is described. Upon addition of strong alkali the fluorescence of the salicylate ion is increased about 9-fold. The blank fluorescence of plasma without salicylate is negligible. The fluorescence is measured directly in a fluorophotometer with the same filters as in the vitamin B1 determination. The fluorescent method offers rapidity and greater sensitivity than previous methods.

## BOOK REVIEW

*Which Way Out*, C. P. OBERNDORF, M.D. New York, International Universities Press, 1948. Price \$3.25.

The author, one of the leaders in the development of psychoanalysis in this country, has adopted the literary device of giving us a glimpse into his personal experiences through the fictional career of Dr. Ben Ford. Truth and fiction are deftly interwoven to illustrate the multitudinous factors that determine the vicissitudes of what ordinarily passes for fate. The stories aptly illustrate the insights into human behavior gained by physicians through the application of Freudian psychology.

This charming collection of stories, written in an easy-flowing style is not burdened with technical expositions. The vivid descriptions and natural quality of the dialogue easily hold the reader's interest to the end. It is a book that will appeal particularly to those who are inquisitive about the inner, hidden drives that influence our lives.

S. MOUCHLY SMALL, M.D.

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## CONTENTS

	PAGE
RESEARCH ON CARDIOVASCULAR DISEASE AND CONGENITAL HEART DISEASE AT THE MOUNT SINAI HOSPITAL. <i>Saul Jarcho, M.D.</i> . . . .	269
THE TECHNIQUE OF CARDIAC CATHETERIZATION AND ANGIOCARDIOGRAPHY AS EMPLOYED AT THE MOUNT SINAI HOSPITAL. <i>Marcy L. Sussman, M.D., Alvin J. Gordon, M.D., Sigmund A. Brahms, M.D., Bernard M. Schwartz, M.D., Arthur Grishman, M.D., Morris F. Steinberg, M.D., and Frederick H. King, M.D.</i> . . . .	272
ELECTROCARDIOGRAPHIC ABNORMALITIES INDUCED BY CARDIAC CATHETERIZATION. <i>Richard P. Lasser, M.D., Raymond Borun, M.D., Alvin J. Gordon, M.D., and Frederick H. King, M.D.</i> . . . .	295
FURTHER EXPERIENCES WITH MICROPLETHYSMOGRAPHY IN THE STUDY OF CONGENITAL HEART DISEASE. <i>Raymond S. Megibow, M.D., and Sergei Feitelberg, M.D.</i> . . . .	303
AORTIC SEPTAL DEFECT SIMULATING PATENT DUCTUS ARTERIOSUS. <i>Frederick H. King, M.D., Alvin J. Gordon, M.D., Sigmund Brahms, M.D., Richard Lasser, M.D., and Raymond Borun, M.D.</i> . . . .	310
ISOLATED INTERVENTRICULAR SEPTAL DEFECT WITH DILATATION OF THE PULMONARY ARTERY, AN ENTITY. <i>Irving G. Kroop, M.D., Raymond Borun, M.D., Richard P. Lasser, M.D., Alvin J. Gordon, M.D., Sigmund A. Brahms, M.D., and Frederick H. King, M.D.</i> . . . .	317
UNCOMPLICATED PULMONARY STENOSIS. <i>Bernard M. Schwartz, M.D., Alvin J. Gordon, M.D., Sigmund A. Brahms, M.D., and Frederick H. King, M.D.</i> . . . .	323
TRICUSPID ATRESIA WITH TRANSPOSITION OF THE GREAT VESSELS: SUCCESSFULLY TREATED BY SURGERY. <i>Sidney Blumenthal, M.D., Sigmund Brahms, M.D., and Marcy L. Sussman, M.D.</i> . . . .	328
ABERRANT INSERTION OF PULMONIC VEINS. <i>Arthur Grishman, M.D., Sigmund A. Brahms, M.D., Alvin J. Gordon, M.D., and Frederick H. King, M.D.</i> . . . .	336
ABSTRACTS . . . . .	344

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RESEARCH ON CARDIOVASCULAR DISEASE AND CONGENITAL  
HEART DISEASE AT THE MOUNT SINAI HOSPITAL

SAUL JARCHO, M.D.

*Associate Physician in Charge of Cardiovascular Research*

As the affairs of The Mount Sinai Hospital returned to normal after the dislocations caused by the second World War, it was recognized that the passage of time and the advance of science required a reorganization of the research activities of the Hospital. The chief need was felt to be an improvement in coordination. To this end it was decided to establish a series of units in those fields of clinical research—such as endocrinology, cardiology, nutrition, and allergy—in which members of the Staff were engaged. In accordance with these ideas, on January 23, 1947, the Research Administrative Committee voted to establish the Cardiovascular Research Group, under the direction of Dr. Marey Sussman. On March 3, 1949, Dr. Sussman was succeeded by Dr. Saul Jarcho.

At the outset it was not deemed desirable to circumscribe the membership of the Group. The Group defined itself, and came to consist of men united by voluntary association and by a common interest in diseases of the circulatory system. The membership evolved chiefly from the following sources: the Medical Services, the Electrocardiography Department, the Pediatric Service, the Service of Thoracic Surgery, the Physics Department, and the X-ray Department. At the outset there were 31 physicians who were connected with projects registered by the Group and who attended meetings regularly.

Inasmuch as the study of congenital heart disease was felt to be a special field of great promise and of great interest to the Hospital, additional administrative mechanisms became necessary. It was decided to establish a single clinic for the ambulatory cases of congenital heart disease, whether in children or adults. It was arranged that Dr. Frederick H. King should be in charge of the Clinic during 1949–1950, and Dr. Sidney Blumenthal would take charge during the academic year 1950–1951. To this clinic all newly admitted patients, regardless of economic status, were to be admitted for preliminary study. This clinic originally met twice each month. The steady increase in the number of patients later made it necessary to introduce a weekly schedule. The clinic is actually housed in the pediatric out-patient building. It is attended by pediatricians, internists, surgeons, cardiologists, and others; recently, a psychiatrist has been added.

The physicians in attendance at the clinic perform the first study of newly admitted cases. Ordinarily this consists of history, physical examination, fluoroscopy of the chest, electrocardiography, and the simpler laboratory analyses. These tests suffice to determine which patients require admission for more extensive study.

After the patient is admitted to the hospital, the Chief of the clinic ordinarily outlines the content and order of subsequent diagnostic studies. These studies may include any of the following: catheterization of the heart with measurement



of intracardiac pressures and determinations of oxygen content; endocardiography; angiocardiography; phonocardiography; microplethysmography; electrokymography; studies of respiratory function; studies of renal function. In cases characterized by extracardiac congenital anomalies, consultations are held with the appropriate specialists.

Very recently a psychiatrist has been added to the staff of the clinic. It will be his duty to observe and report the effects of the congenital disease upon the psyche of the patient. He will also be required to protect the patient as far as possible against psychic traumata incident to the elaborate diagnostic studies and treatments which are applied in cases of congenital heart disease.

In cases considered suitable for operative treatment, one member of the clinic is made responsible for the day-to-day welfare of the patient. The physician selected for this purpose is expected to visit the patient daily from the time of admission to the time of discharge. For private patients this function is usually carried out by the referring physician.

In ward cases it has been customary not to admit the patient to the surgical ward directly. Instead the patient first enters the wards of the pediatric service or medical service. Not until completion of the diagnostic study does the patient gain admittance to the surgical service. After the immediate postoperative period the patient is usually returned to the service of origin, where final studies are performed, and the final case summary is written. When the patient is discharged from the wards, arrangements are made for follow-up visits to the congenital heart disease clinic.

Attendance at the clinic and the performance of various diagnostic procedures by no means complete the roster of the physicians' activities. Most members of the Cardiovascular Research Group also find the time and energy to engage in research problems dealing with various aspects of circulatory function in health and disease. The following are examples of recent research projects:

Sussman, M.; Gordon, A.; Fettelberg, S.; and Brahms, S.: The diastolic volume of the right ventricle.

Megibow, R.: Plethysmographic studies.

King, F. and Schwartz, B.: Pressure determinations in the right heart.

Grishman, A.; Kroop, I.; and Steinberg, M.: Atrial preponderance.

Sussman, M., Dack, S., and Paley, D.: Electro-kymography.

Blum, L. and Megibow, S.: Exclusion of the right heart by mechanical extra-corporeal shunts.

Mendlowitz, M. and Parets, A.: Calorimetric studies of digital blood flow.

Kisch, B.: The nature of the first heart sound and its relation to the endo-cardiogram.

Friedberg, C.: Electrolytes in heart failure.

Sirota, J.: Studies on renal function.

Each research project must receive initial authorization at a meeting of the Research Administrative Committee. Authorizations ordinarily are valid for one year only. At the end of a year the experimenters submit to the Committee a detailed report of their work. If the report is satisfactory and the work is deemed

promising, an extension of time is granted. In this manner all projects are under continuous surveillance, and all members of the Research Administrative Committee are made acquainted with the progress of each investigation.

The work of the Cardiovascular Research Group and of the Congenital Heart Disease Clinic is supplemented by an elaborate program of conferences and meetings. Thus, the Tuesday afternoon meeting of the Congenital Heart Disease Clinic is usually concluded by a conference at which the more interesting new cases are discussed. During most of the season of 1949-50 there were, in addition, biweekly meetings on congenital heart disease. These were held in the Blumenthal Auditorium, and ordinarily consisted of two or three elaborate case presentations. In addition, there were monthly meetings which gave opportunity for prolonged discussion and for the presentation of special research reports. Examples of such reports are the following:

Sirota, J.: Observations on renal function.

Kroop, I.: The technique and results of esophageal electrocardiography.

Mendlowitz, M.: Principles and technique of calorimetry as applied to the study of the circulation.

On January 16, 1950, a special clinical conference on congenital heart disease was held in the Blumenthal Auditorium. After introductory remarks by Dr. George Baehr, six papers on various aspects of congenital heart disease were presented. In each instance the presentation of the case was made by a member of the House Staff of the hospital. Elaborate discussions were then presented by members of the Cardiovascular Research Group. The papers which compose the present Symposium are based largely on this material. Some degree of amplification has been permitted in the preparation of material for publication. This amplification has made possible participation by some members of the Group who could not be included in the program presented at the Auditorium. The material being published is intended to represent most of the phases of the work which is being done by the Cardiovascular Research Group and the Congenital Heart Disease Clinic.

It will at once be apparent to the observant reader that the material presented could not have been developed without a high degree of cooperative integration. In some instances, indeed, the cooperation has been so complete and effective that it has been difficult to assign exact credit for authorship. The Director of the Cardiovascular Research Group has attempted to err, if at all, on the side of inclusiveness; and he hopes that no participant has been overlooked.

## THE TECHNIQUE OF CARDIAC CATHETERIZATION AND ANGIOCARDIOGRAPHY AS EMPLOYED AT THE MOUNT SINAI HOSPITAL<sup>1</sup>

MARCY L. SUSSMAN, M.D.,<sup>2</sup> ALVIN J. GORDON, M.D., SIGMUND A. BRAHMS,  
M.D., BERNARD M. SCHWARTZ, M.D., ARTHUR GRISHMAN, M.D., MORRIS  
F. STEINBERG, M.D., AND FREDERICK H. KING, M.D.

### INTRODUCTION

Angiocardiography was begun in this hospital in 1939, shortly after the procedure was introduced into the United States (1). Cardiac catheterization was started in the winter of 1947. From the very first it seemed logical to combine the two procedures in the diagnosis of congenital heart disease. Experience has proved that complications were not increased when this was done. We have employed the combined procedure routinely in cases in which both examinations were indicated. On rare occasions catheterization has been terminated because the catheter could not be passed or because the patient was reacting unfavorably. In some of these instances angiocardiography was performed; in others, it was postponed.

Up to now angiocardiography has been performed approximately 2,000 times at The Mount Sinai Hospital. One hundred and twenty-five catheterizations have been performed; of these the great majority were followed immediately by angiocardiography. The youngest patient upon whom both procedures were successfully performed in a single examination was fifteen months old.

In general, we have followed the catheterization technique used by Cournand and associates (2). The technique of angiocardiography has been the result of gradual development since its inception eleven years ago. Our methods have undergone numerous modifications and improvements during these years. It is felt that a detailed description of our present technique may be useful.

*Preparation of the patient for the combined procedures:* Adults are given a light breakfast and no lunch. The procedure is begun at 1 P.M. One and one half grains of sodium pentobarbital are often given one to two hours beforehand, especially if the patient is apprehensive. The amount of information to be given to the patient in advance depends upon the individual concerned.

*Children:* It has been our policy to induce general anesthesia in all children under the age of eleven and in some older ones, as determined by the child's behavior on the ward. A cleansing enema is given the night before and again on the morning of the procedure. No food or drink is allowed all day. Sodium pentothal is given on the ward at 12:30 P.M. The dose is 1 gm. per 75 lbs. of body weight, given rectally in 10% solution. Fifteen minutes later the child is

<sup>1</sup> From the Cardiovascular Research Group and the Department of Radiology, The Mount Sinai Hospital.

Aided by grants from the Isaac Schneierson Foundation, the Dazian Foundation for Medical Research and the Linde Air Products Company.

<sup>2</sup> Now of Phoenix, Arizona.

brought to the catheterization room and at 1 P.M. given rectal Avertin, in the dose of 90 mgm. per kilogram of body weight. If the anesthesia wears off during the catheterization, a second dose of 50 mgms. per kilogram may be given. At the completion of catheterization, the patient is anesthetized with ether by the open mask drop technique, the catheter is withdrawn, the cannula inserted into the same vein, and the angiocardio-gram performed.

Unless there is some contraindication, all patients are given procaine penicillin on the morning of the procedure and perhaps twenty-four hours later, as prophylaxis against subacute bacterial endocarditis and local infection.

#### CATHETERIZATION

*The team:* The catheterization team consists of the surgeon, the fluoroscopist, the man in charge of the galvanometers, and the recorder. The latter two duties may be performed by one individual, if he is experienced. In addition, the oxygen technician may be present to receive the blood specimens. The four physicians rotate in their duties as much as possible.

*The records:* A detailed and complete protocol is kept of the procedure, notations being made of each step on a mimeographed form. A separate line is taken for each observation or series of observations at any particular location of the catheter. The next day, when all results are available, there is a meeting of the group to discuss the findings, and the final reports are made.

*The work room:* At the present time the catheterization and angiocardio-gram are done in adjacent rooms in the x-ray department. The catheterization is performed on an x-ray table. A thin, foam-rubber mattress is used, which is comfortable for the patient, but does not interfere with the fluoroscopy or spot films. Several members of the group are furnished with red flashlights so as not to disturb the fluoroscopists.

*Protection from radiation:* The amount of radiation to which both patient and physician are exposed during catheterization and angiocardio-graphy may be considerable (3).

Fluoroscopy is kept to a minimum and the field made as small as possible consistent with adequate guidance of the catheter. The factor of five m.a. is never exceeded. Sixty-two k.v. are used in children and sixty-seven k.v. in adults. A limit of ten minutes is placed upon actual fluoroscopy time and is controlled by an automatic timer. If completion of the procedure is in sight, an additional two minutes is allowed.

All members of the team wear heavy lead-impregnated aprons. The fluoroscopist wears lead-impregnated gloves. The surgeon dons his protective apron before scrubbing. While the surgeon manipulates the catheter, his hands receive additional protection from our specially designed plywood and lead shield fitted with a lead rubber apron.<sup>3</sup> This device is placed on the table between the patient's arm and his chest.

*Precautions to maintain sterility:* To maintain sterile technique Merthiolate solution (1:2500) is kept in the strain gauge and flushed out with sterile saline

<sup>3</sup> Made for us by the Bar-Ray Products Company, Brooklyn, N. Y.



before use (see below). The sterile stopcock manifold must be attached to the unsterile receiving stopcock of the strain gauge (fig. 1). However, none of the saline within the gauge flows directly into the catheter. The fluoroscopic screen must be kept from contact with the sterile operative field or the catheter, especially during manipulations in the dark.

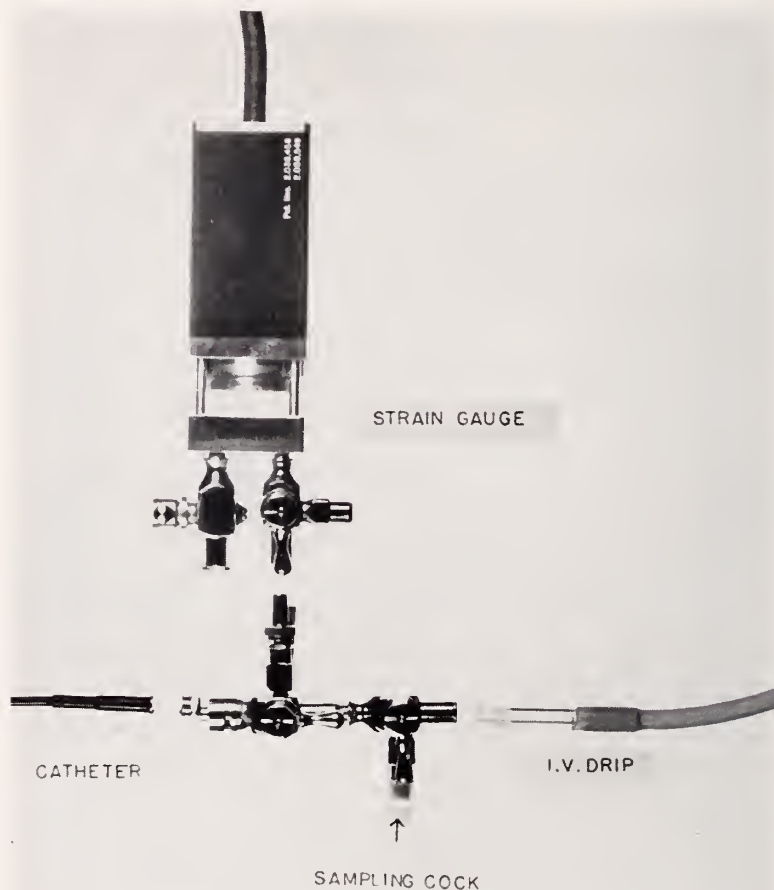


FIG. 1. A view of the strain gauge and stopcock manifold to show details of catheter and intravenous attachment and sampling cock.

The instruments and syringes used in catheterization are autoclaved en masse in a metal container. The operative table contains the following:

- 2 500 c.c. beakers (one for clean heparinized saline and one for waste)
- 3 20 c.c. syringes, preferably Luer-Lok type (for flushing through the catheter)
- 10 5 c.c. syringes (for cardiac samples)
- 2 2 c.c. syringes (for local anesthesia)
- 1 L-shaped graduated tube, of the type used for direct determination of venous pressure

2 #26 needles, 2 #20 needles

Skin needle and silk thread

Several large safety pins (should a syringe tip break off in the sampling cock, the point of a safety pin is used to remove it.)

2 small mosquito hemostats

2 small mouse-tooth forceps

2 large curved hemostats

1 needle holder

2 scalpels, one with standard blade, one with #11 blade

6 towel clips

1 small serrefine clamp

1 vein spreader (to be described below)

1 special stopcock manifold (to be described)

Sterile towels, sterile gauze squares

Sterile tourniquet

In addition, sterile drapes, gowns and gloves are available. Alcohol, peroxide, Metaphen, 2% sterile procaine solution, heparin solution (Liquaemin—10 units per c.c.), mercury in a dropper bottle and hydrogen peroxide are needed. The catheter, arterial needle, and intravenous set complete the inventory.

*Choice of the vein:* Since the majority of our angiocardiograms are performed in the left anterior oblique position, it is most convenient to use a right antecubital vein. Unfortunately greater difficulty is experienced in entering the superior vena cava and in performing manipulations within the heart from this site. If an angiocardiogram is not planned, or if the postero-anterior position is to be used, the left arm is used. A large vein in the antecubital fossa is sought which courses medially toward the basilic vein. It is often impossible to enter the thorax through veins entering the cephalic system. In children under four or five we prefer to use the saphenous vein even when an arm vein of sufficient size is present. We have the impression that there is more likelihood of traversing an interatrial septal defect from below. On the other hand, greater difficulty is experienced in entering the right ventricle and pulmonary artery.

*Arterial samples and pressures:* Samples are taken and pressures are measured from either the brachial or femoral artery in adults. In children the femoral artery is usually used. If it is only desired to take blood samples for oxygen analysis, a  $1\frac{1}{2}$  inch #20 needle is used, attached to a syringe. A single pressure tracing may also be taken with this technique, by interposing between the needle and the syringe a three way stopcock equipped with a short length of polythene tubing as a side-arm. When repeated determinations or samples are desired, an indwelling needle is used—the Cournand needle for adults and the Riley needle for children. The latter is similar to the Cournand needle but is smaller (#20) and has a solid obturator in place of the needle-stylet of the Cournand needle.

In order to avoid the leakage of blood that occurs when the obturator is removed from these needles for repeated determinations, it is sometimes preferable to maintain a slow continuous infusion into the arterial needle. The infusion set, arranged to deliver the saline under pressure, is connected to a special

double stopcock (see below), which in turn is connected to the arterial needle by means of a short length of polythene tubing. Arterial pressures may then be registered, or samples of blood taken through the stopcock, after temporarily shutting off the infusion.

It should be noted that an ordinary glass-tipped syringe will not fit into the hub of a Cournand needle. Either a Luer-Lok or a Bishop Sempra syringe with a large-bore tip must be used. The technique of passing the indwelling arterial needle is described in detail in the monograph by Drs. Cournand, Baldwin and Himmelstein (2). We can confirm the experiences of others (4) who on rare occasions noted syncopal reactions in patients in whom insufficient local anesthetic was used. Thrombosis of an artery following needling has not occurred in our series.

Special arterial needles demand great care in cleaning and storage. The stylet-needle of the Cournand needle, in particular, is difficult to keep patent. For cleaning these needles we have used either hydrogen peroxide or the detergent solution used for cardiac catheters (see below). Each needle is autoclaved in its own container. We have used small flat-bottomed Pyrex jars for this purpose (Machlett—A66-340). These have the advantage that when the needle is removed the jar may be used for the peroxide in which to place the stylet when not in use.

For arterial pressures we have used a strain-gauge transducer of  $\pm 4$  pounds per square inch (200 mm. mercury) range (Statham model -P23). The connection between the intra-arterial needle and the gauge is made by lead tubing or by a short length (10–15 cm.) of polythene tubing (5) to each end of which an adapter has been fitted.

The polythene tubing<sup>4</sup> has an inside diameter of 0.125 inches and an outside diameter of 0.15 inches. By immersing the end in boiling water for a few minutes it can be softened sufficiently so that it may be stretched by a tapered metal object and fitted over the hose-end of an adapter (such as the Becton-Dickinson #607/L) or of a three-way stopcock (such as the L/S stopcock made by the same company). One end of the connecting tube thus fashioned may be slipped into the hub of the indwelling arterial needle, and the other into the stopcock of the strain gauge. Such connections are sufficiently tight for the purpose.

Polythene tubing may not be sterilized by boiling or autoclaving as it is thermoplastic. We have used cold sterilization by prolonged immersion in 1:2500 Merthiolate solution. After use, there is a tendency for a thin film of blood to remain on the inside of the tubing; this may be removed by means of a pipe cleaner.

Polythene tubing is easier to bend and manipulate than lead but still has sufficient resistance to stretching to give adequate pressure curves.

*The intracardiac catheter:* The Cournand intracardiac catheter<sup>5</sup> is made of a hollow nylon core covered with several layers of plastic material. We prefer the "birds-eye" tip (6) because there is less difficulty in obtaining blood samples, and pressure records show fewer artefacts. For tall patients a catheter 125 cm. long is used, rather than the standard length of 100 cm. Sizes 6F and 7F have been most satisfactory from every standpoint.

*Cleaning:* After use the catheter is flushed repeatedly with water. Once blood

<sup>4</sup> Made by the Suprenant Co., 199 Washington St., Boston, Mass.

has been allowed to clot within the catheter, it can rarely be removed completely. The catheter is immersed for 20 minutes in the following cleaning solution, which is also flushed through the catheter repeatedly with a syringe:

- 1 c.c. Detergicide<sup>5</sup>
- 1 flat teaspoonful Calgon (sodium hexametaphosphate)
- 1 quart of water.

The hub is then attached to a filter pump and tap water drawn through under pressure for at least five minutes, followed by a large amount of pyrogen-free distilled water. Care must be taken that the detergent solution is completely washed off the outside of the catheter, as well as the inside. If it is not, the catheter will feel slippery to the touch.

*Sterilization:* We used cold sterilization at first but found autoclaving more satisfactory.

The catheter is fed into a long kraft-paper envelope made by us for this purpose. To facilitate removal from the envelope, a length of coarse string is knotted around the hub of the catheter and one end of the string is brought out through the envelope. The envelope is then sealed and autoclaved for five minutes at 250°F under 20 pounds of pressure. The catheter may then be used at any time up to three months after sterilization. The chief difficulty with this method of sterilization is that the catheters tend to lose their terminal curve. To restore the curve the catheters may be autoclaved with shaped stainless steel stylets in place. We have used Malin's Stainless Wire, #13, diameter 0.031 inches for #6F and #7F catheters. For #8F and #9F catheters #18 wire, diameter 0.041 inches is satisfactory. The tip of the wire must be polished carefully before it is inserted into the catheter to prevent injury to the nylon lining.

Needless to say, the catheters should be carefully checked for leaks and imperfections before use.

*Pressure transducer and recording system:* Direct recording of intracardiac and intra-arterial pressures are made by means of Statham (strain) gauges and a four-channel single speed direct-writing electrocardiograph (Fig. 2) which has been converted in such a way that the upper channel records intracardiac pressures and the second intra-arterial pressures or intraventricular pressures if a double-lumen catheter is used. The latter channel may be used alternatively to record one of the electrocardiographic leads. The third and fourth channels record electrocardiograms, including an endocardial lead if desired.<sup>6</sup> (Fig. 3). A direct writing instrument such as this has obvious advantages but produces curved vertical coordinates, resulting in distortion of wave form. This is partially compensated by the use of paper with curvilinear vertical coordinates. Distortion has usually caused no difficulty.

Electrical and mechanical events within the heart, when measured on our records, fall within the normal values established by Coblenz et al. (7).

*Intracardiac pressures:* For catheter recording a Statham<sup>7</sup> gauge of  $\pm 15$

<sup>5</sup> Manufactured by the U. S. Catheter and Instrument Co., Glens Falls, N. Y.

<sup>6</sup> We are grateful to Mr. Martin Scheiner, formerly chief engineer of the Electrophysical Laboratories, N. Y. for the development and maintenance of this instrument.

<sup>7</sup> Statham Laboratories, Beverly Hills, California.



pounds per square inch range ( $\pm 780$  mm. of mercury) is employed. (Fig. 1) (Models P23 and P23A). Since the maximum pressures to be measured are of the order of 50 to 100 mm. of mercury, a carrier-type amplifier is used which also contains the source of power to actuate the transducer. Sensitivity of the amplifier is better than 5 cm. deflection per millivolt input, so that maximum

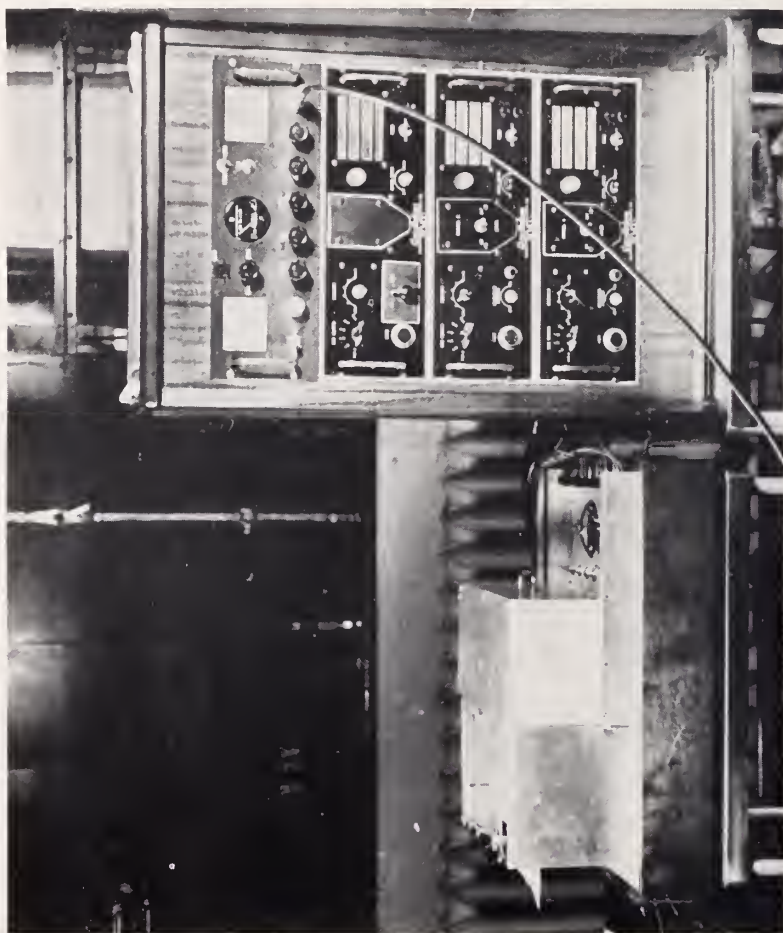


FIG. 2. The four-channel direct-writing electrocardiograph used in our studies. The control panel is on the right, and the recorder on the left. The battery box which actuates the strain gauge for channel two is not shown.

deflection sensitivities of 2 mm. deflection per mm. of mercury pressure are readily obtained. Sensitivity may readily be decreased to a minimum of one mm. deflection per 5 mm. of mercury pressure, or even less, if desired. Carrier frequency is 1000 cycles per second. The frequency response of the amplifier is flat from zero to over 50 cycles per second. However, the frequency response of our combined system has not been tested. According to the manufacturer of the pressure transducer (8) the frequency response of a no. 6F 100 cm. long

catheter attached directly to the P23A transducer is essentially flat up to a frequency of 50 cycles per second. This would indicate that our system is fairly accurate. Our records, at any rate, appear very similar to those obtained with

## NORMAL TRACINGS

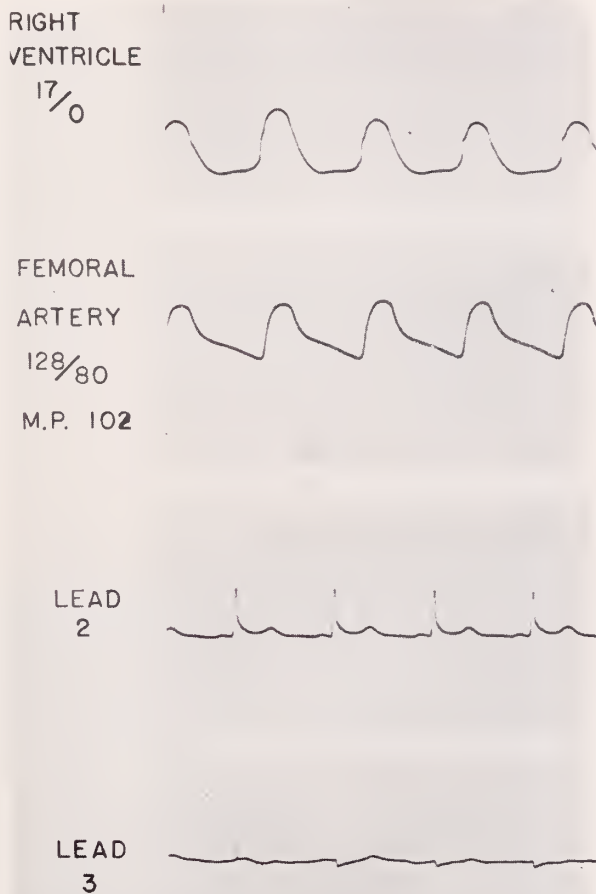


FIG. 3. Four-channel tracing taken during cardiac catheterization, showing time relationships of normal right ventricular and femoral artery pulse.

other systems of presumably higher frequency response (9, 10). Although the frequency response should improve as the diameter of the catheter increases (11), we have obtained smoother and probably more accurate curves with the smaller catheters. This is probably due to the greater relative rigidity of the wall of the latter (12). Normal and abnormal pressure curves are shown in the illustrations (Figs. 4-9).

Curves from the pulmonary artery are most likely to show artefacts. It is

often necessary to manipulate the catheter tip from place to place until a good tracing is obtained.

*Intra-arterial pressures:* For arterial pressures a Statham gauge of  $\pm 4$  pounds per square inch range (200 mm. of mercury) is used, in conjunction with a direct-coupled amplifier to give a maximum sensitivity of about 1 mm. deflection per

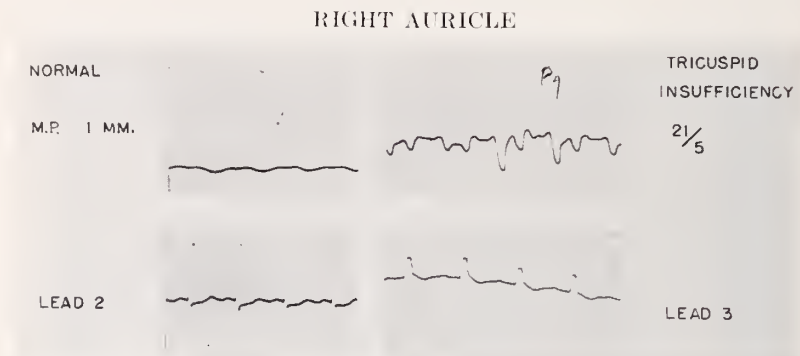


FIG. 4. Normal and abnormal right auricular pulse tracings. In the normal tracing on the left there is a succession of double waves, of which the first is associated with ventricular systole (V-wave) and the second with auricular systole (A-wave). The closure of the tricuspid valve is not reflected in these tracings. In the case of tricuspid insufficiency the most characteristic finding is the plateau-like interval during ventricular systole, caused by regurgitation from the ventricle (10).

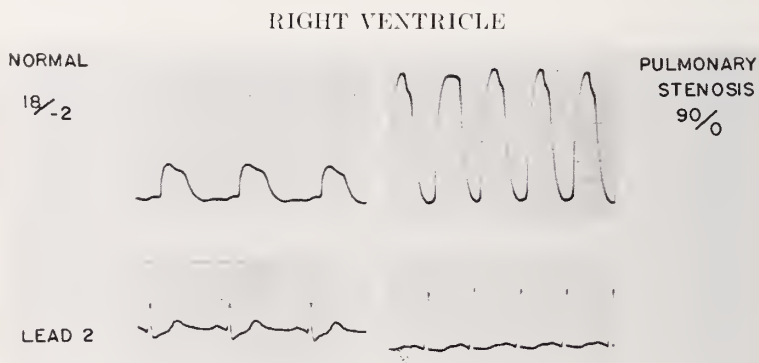


FIG. 5. Normal and abnormal right ventricular tracings compared.

5 mm. of mercury. The sensitivity of this channel may also be decreased. This gauge is actuated from a conventional dry battery source.<sup>8</sup> Galvanometers on all channels are provided with electrical damping by means of a feed-back coil.

Both pressure panels are provided with a standardization button. On the top channel it produces an electrical output equal to an applied pressure of 20 or

<sup>8</sup> A control unit is available from the manufacturer, which contains all the electrical adjuncts required to connect the gauge to any suitable indicator or recorder, such as a standard electrocardiogram.

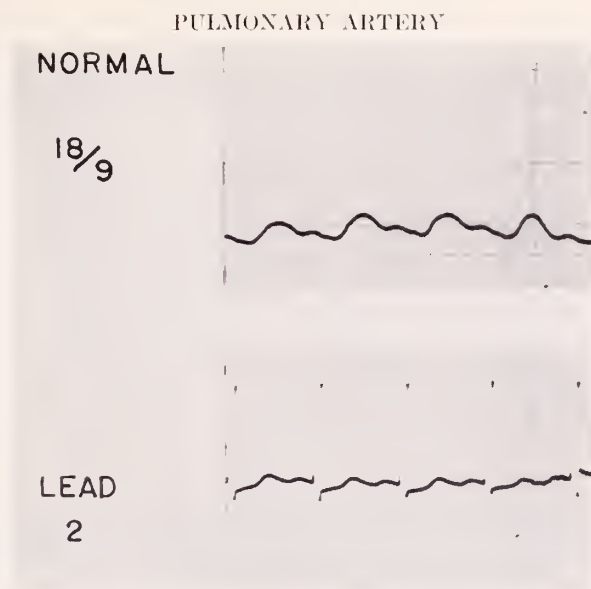


FIG. 6. Normal pulmonary artery tracing.

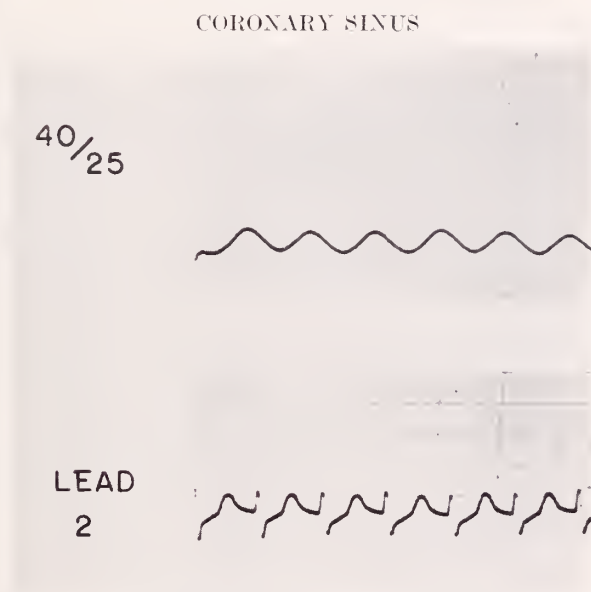


FIG. 7. A characteristic pressure tracing from the coronary sinus.

30 mm. of mercury and on the second channel equal to 100 mm. of mercury. This button is used only to give a rough index of the sensitivity. At the end of the catheterization each gauge is calibrated at each sensitivity used by means of an aneroid manometer which is checked frequently against a mercury mano-



## PULMONARY HYPERTENSION

(?EISENMENGER'S COMPLEX)

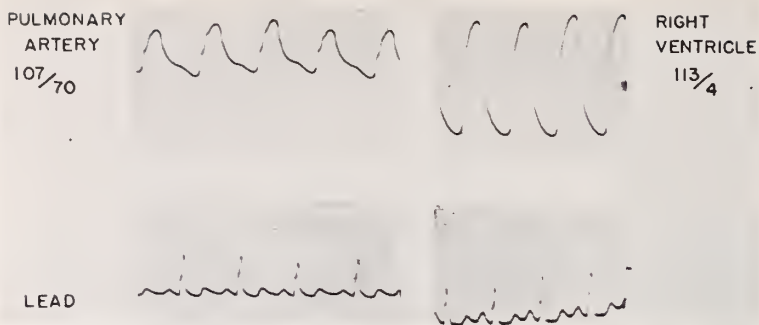


FIG. 8. Tracings from the pulmonary artery and right ventricle in a case of pulmonary hypertension. The diagnosis was either Eisenmenger's complex or primary pulmonary arteriosclerosis.

## COARCTATION OF AORTA

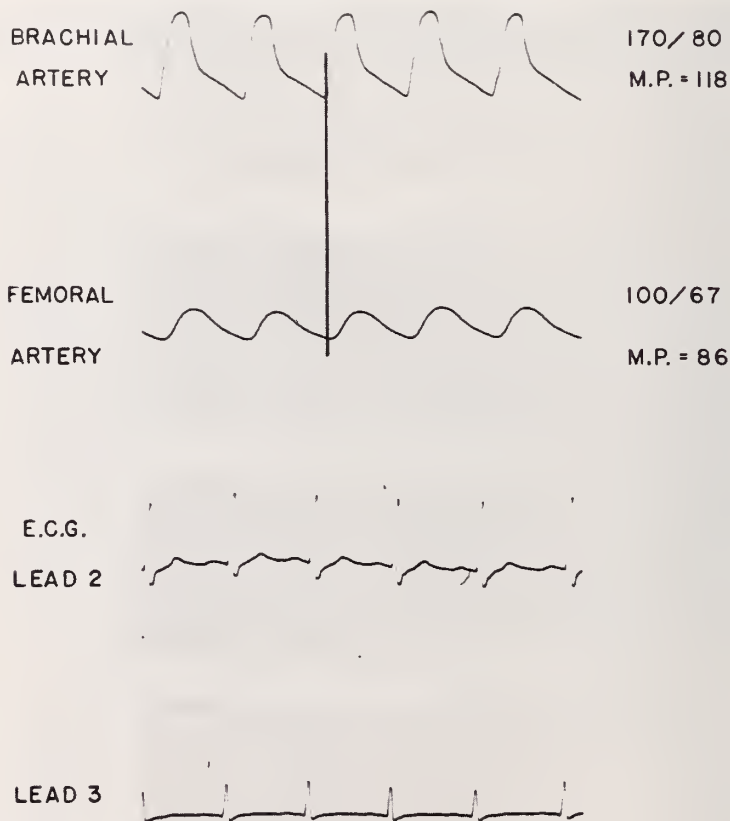


FIG. 9. Simultaneous brachial and femoral artery tracings in a case of coarctation of the aorta. The heavy vertical line was drawn to emphasize the delay in the onset of the systolic rise of the femoral pulse.

meter. The accuracy of intracardiac tracings taken in low-pressure areas is sometimes checked during the catheterization by attaching an L-tube water manometer to the blood sampling cock and determining the mean pressure in terms of water. We believe this to be an accurate measure of pressure provided sufficient time is allowed for equilibrium to be reached. Ideally the calibration of the gauges for low pressures should be made with water rather than mercury. We have recently installed a panel containing a mercury and a water manometer, connected by a three-way stopcock so that either may be used for calibration.

In order to avoid error due to drift of the base line the zero line is adjusted by opening the gauge to the atmosphere before each pressure reading.

In order to connect the catheter to the strain gauge on the one hand, and to the intravenous solution on the other, and still have a cock left for taking blood samples, it has been necessary to construct a combination instrument (designed by S. A. B.) in which two special three-way stopcocks are soldered together (fig. 1).

These stopcocks must be handled with care. After completion of the catheterization they are cleaned with the same solution that is used for the catheters. In time they become "stiff". They must then be unscrewed, the parts immersed in a solvent such as carbon tetrachloride and then dried. A thin film of stopcock grease is placed around the bore of the cock and the parts reassembled. When cleaning more than one stopcock it should be remembered that the parts may not be interchangeable.

*Endocardial electrograms:* One of several methods may be used to obtain endocardial leads during routine catheterization of the heart:

1. A special double-lumen catheter may be used, in one lumen of which an electrode is permanently sealed.<sup>9</sup> This catheter has an outside diameter equivalent to 9F, is relatively rigid and is too large for use in children.

2. An adequate record may sometimes be obtained by clamping the lead wire to the metal hub of an ordinary catheter (13). The column of blood or saline in the catheter then acts as the conducting medium. Records obtained in this way, unfortunately, are subject to interference artefacts (13, 14).

3. A very fine wire may be incorporated into the catheter lumen in such a way that one end reaches to within a short distance of the tip, and the other end is brought out through a tiny hole drilled in the metal hub and soldered to the outside (13). This method probably interferes to some extent with pressure recording and with ease of blood sampling.

4. The same effect may be achieved by soldering one end of the wire to the inside of a Luer-Lok adapter (15). This makes a removable electrode which is nevertheless airtight when screwed into the catheter.

5. A special combination catheter electrode has recently become available<sup>9</sup> in which the electrode is incorporated in the catheter wall without compromising the lumen. This catheter is made in different sizes.

For use as a removable wire electrode we have found stainless steel or nickel-chromium alloy, B. and S. size #28, diameter .012 inches, most satisfactory.

<sup>9</sup> Available from the U. S. Catheter and Instrument Company.

Larger sizes increase the rigidity of the catheter, whereas smaller ones are difficult to thread through the catheter.

*The intravenous set:* We have used normal saline solution in a one liter bottle with a tight-fitting rubber stopper provided with two thin rubber diaphragms. A long hollow glass rod is fitted under one of these, which acts as the air intake. The other diaphragm is designed for the tubing assembly.<sup>10</sup> The needle adapter on the other end of the infusion set fits into the end of the special stopcock described above (Fig. 1). After the intravenous set is assembled and hung on its pole, an aneroid manometer and bulb assembly are attached to the air intake needle to increase the pressure within the bottle when necessary (i.e. when the catheter tip enters an area within the heart in which the pressure exceeds that of the column of saline). It is apparent that the infusion bottle and tubing must be able to withstand a pressure of 100 mm. of mercury or more.

*The catheterization in detail:* After scrubbing, the operator dons sterile gown and gloves. He removes the rubber stopper from the bottle of saline, and pours 500 cc. into the first sterile beaker on the operating table. He then adds one cc. of heparin (Liquaemin, Roche-Organon, 1 cc. equals 10 mg.) to this beaker, and one cc. to the saline in the bottle. The stopper is replaced, the intravenous tubing and the air intake needle attached, and the bottle is hung by an assistant, who then attaches the pressure bulb and manometer.

The operator prepares the syringes for cardiac sampling by withdrawing the plunger, adding several drops of heparin solution (as above) and two drops of mercury. The plunger is replaced and the dead space filled with the heparin and mercury. An extra drop or two of solution is left in the syringe, to be expelled just before sampling. We have not found it necessary to use mineral oil to prevent leakage of air. Recently, we have used Bishop Semptra syringes for cardiac samples. These have interchangeable barrels, and metal tips. Furthermore, their shape is such that it is easier to expel the air from their tips.

An assistant clamps the strain gauge in place. For this purpose we have used ordinary chemical apparatus clamps of large size, fitted with thick rubber sleeves. The clamps attach to the intravenous pole which must be of small enough circumference to accommodate them. The gauge is placed at a level five cms. posterior to the angle of Louis. The intravenous set is attached to the special stopcock and the latter, to the gauge. An assistant expels all air from the gauge. The operator attaches the catheter after carefully inspecting it.

The patient is brought in, the electrocardiographic electrodes attached, the skin sterilized and draped. (It is wise to mark the site of the vein with waterproof ink beforehand). It has been our custom to incise the skin at right angles to the vein. In the case of the saphenous vein a transverse incision about one inch in length is made  $1\frac{1}{2}$  inches below Poupart's ligament and just medial to the femoral artery. It is sometimes necessary to cut away subcutaneous fat to improve the exposure. The saphenous vein usually lies deep to a thin but discrete strong layer of fascia. If difficulty is encountered in finding a vein in the arm,

<sup>10</sup> We use the Continental Stat 17R Transfusion set, made by the Continental Pharmacal Co., 1400 W. 25th St., Cleveland, Ohio.

application of a tourniquet may help considerably. Dissection should be blunt, and usually is performed with the small hemostat.

After the vein is isolated, it is stripped of fatty tissue and fascia and a ligature is placed as far distally as possible. The vein is grasped proximally to this ligature with a fine mouse-tooth forceps, which is then elevated out of the wound. The scalpel with the #11 blade is held with the blade facing upward and parallel to the floor and the vein is partially incised at right angles to its long axis. It is better to err on the side of a smaller rather than a larger incision in the vein, since if the vessel is cut across or tears across, it can seldom be retrieved. If the vein appears small and delicate to begin with, and tributaries are present, it is wise to tie the latter but not to sever them, so that the tie may be used to retrieve the larger vessel should it be severed and retract.

When the catheter tip is passed into a vein without the aid of special instruments, the tip should be directed straight down into the incision in the vein, thereby entering the vein at right angles and distending the opposite wall. Only then should the direction of the tip be changed so as to progress upward in the vessel.

To facilitate passage of the catheter into the vein we have used an instrument made by one of us (S. A. B.) which is a fine-pointed forceps with sharply curved tip. A similar device has been described elsewhere (16). The spread is controlled by a set-screw. After the vein has been incised with the scalpel, the closed forceps is introduced into the vein and allowed to separate. It is shifted to the left hand, and the ligature anchored as well as possible by the little finger of the left hand, thus creating a triangular opening in the vein into which the catheter usually slips with ease. With this instrument we have been able to pass catheters into very small vessels. Usually these vessels distend to accommodate the catheter.

Occasionally *venospasm* occurs, and appears to bear no relation to the size of the vein. We have been unable to release it with local heat or procaine or by running fluid into the catheter under pressure. Certain patients seem predisposed to the development of venospasm. In one instance, it occurred on two separate occasions in the same subject. In this patient, an adult woman, it was impossible to pass the catheter into the chest through an arm vein, although the veins were very large. A saphenous cut-down had to be done. Occasionally venospasm may develop during the catheterization. When this happens, an attempt should be made to pass the catheter quickly as far as possible, before forward progress is prevented completely. When spasm of the vein occurs, manipulation of the catheter becomes painful.

Occasionally excessive bleeding occurs around the catheter, particularly if the venous pressure is high or if the incision in the vein is too large. This may best be controlled by passing a silk thread around the vein proximal to the opening, and tying it loosely in place. If it is not too tight, it will control the bleeding without impeding the progress of the catheter.

As soon as the catheter has entered the vein the intravenous drip is started and the catheter is passed toward the axilla and into the chest, if possible. The remainder is performed under fluoroscopic control.



If difficulty is encountered in passing the catheter into the thorax, the arm is abducted, the head turned to that side, or the shoulder raised off the table. In all manipulations of the catheter it is twisted so that the point is directed properly and repeated rapid probings are made until the desired result is obtained. Frequently, (especially when the procedure is performed from the right side) the catheter will enter the thorax but fail to enter the superior vena cava, crossing over into the left innominate vein or passing upward into the internal jugular vein on the same side. Repeated trials may be necessary to enter the superior vena cava. The process may be facilitated by having the patient inhale deeply. The latter maneuver often causes the catheter tip to point further downward.

After the tip has entered the right auricle the glowing stylus of the electrocardiograph is watched for disturbances of rhythm, particularly premature contractions. This is the responsibility of the member of the team in charge of the galvanometers. It is his duty to warn the operator of electrocardiographic changes. The same man watches the intravenous drip, adjusting the flow or applying pressure as needed. As soon as the tip enters the right ventricle the intravenous drip is checked, as increased pressure is usually needed at this time, if at all.

It is sometimes difficult to enter the right ventricle, even more so the pulmonary artery. Occasionally the coronary sinus may be entered although the operator may believe the catheter to be in the right ventricle (15). However, the course of the catheter is fairly characteristic, and the pressure pulse may be (Fig. 7); the tip cannot be advanced beyond a certain point, and the blood from the sinus is very dark. This may be apparent on gross inspection, before the oxygen content is known. In many cases of pulmonary stenosis the pulmonary artery cannot be entered.

If difficulty is encountered in identifying the position of the catheter, the pressure tracing is of greatest value. Occasionally a continuous pressure record is made as the catheter is slowly withdrawn—this maneuver may be of aid in identifying the chambers through which the tip passes. Finally, as mentioned above, the oxygen content of the blood may be the decisive factor; frequently an estimate can be made from the color alone. Spot x-ray films should be made when doubt exists as to the location of the catheter.

A stiff catheter may soften from prolonged manipulation at the temperature of the blood stream. When difficulty is experienced in directing the catheter, occasionally a change of catheter, selecting a different size or one with a different curve at the tip, will be useful. We have had no experience in the use of steel stylets to stiffen the catheter during manipulation (17).

Occasionally, when a large stiff catheter is used, the mobility is impaired by having the hub fixed to the gauge assembly. The stopcock manifold may then be disconnected from the gauge, although still attached to the intravenous tubing on one end and the catheter on the other. It may then be reattached whenever it is necessary to record a pressure.

*Collecting the cardiac samples:* With the beam from a small flashlight fixed on it, the 20 cc. Luer-Lok syringe, partly filled with the heparinized saline from the beaker, is attached to the sampling cock and slight suction applied until

blood shows in the syringe. About three cc. of blood is aspirated, the syringe replaced by the one prepared with heparin and mercury, and the sample withdrawn, *using gentle suction at all times*. If too much negative pressure is produced, air may enter the syringe from around the plunger. In addition, ventricular premature contractions may occur if the tip is in the right ventricle. Our average sample amounts to 2 or 3 cc. although satisfactory determinations may be made on as little as 1 cc. of blood.

A single medium-sized bubble is often present. This is immediately expelled by an assistant, a short rubber sleeve is slipped over the tip of the syringe, and the open end sealed with a small glass rod. If foam forms in the syringe, the sample is discarded. The syringes containing cardiac samples are rotated to promote mixing and stored vertically with tips down in an ordinary test tube rack which in turn is placed in a large container of cracked ice and water.

The blood is analyzed for oxygen by the method of Roughton and Scholander (18) and corrections made for dissolved oxygen (19). No correction is made for the dilution of the blood by the heparin solution in the syringe. Each analysis is done in duplicate and the two values required to check within 0.2 volumes percent. The analyses should be done as promptly as possible. On occasion it has been necessary to wait overnight. In many cases analyses repeated twenty-four hours later have given acceptable checks, but this cannot be depended upon. At times our values for arterial oxygen saturation have been slightly lower than those usually accepted (20, 21).

We have not routinely measured oxygen consumption during the catheterization. On occasion we have measured the basal metabolic rate on the morning of the procedure, calculating oxygen consumption from that figure. In most cases we have been content to measure shunts as a percentage of the systemic flow (2).

*Complications of catheterization:* We have had no deaths or serious reactions to cardiac catheterization. Frequent ventricular premature contractions, often resulting in short runs of ventricular tachycardia, are very common; indeed, the more carefully they are sought, the more frequently are they found. They occur when the catheter is being manipulated in the right ventricle, or when the right atrium is stretched by a coiled catheter, when the latter is fairly rigid. Manipulation on either side of the tricuspid valve, or stimulation of the interventricular septum are apt to cause them. Despite these premature contractions, we have occasionally continued to manipulate the catheter for a short time, and have found that if the catheter tip enters the pulmonary artery, the arrhythmia stops (22). A run of ventricular tachycardia has never continued for more than a few seconds after the catheter was withdrawn into the right atrium provided it was not coiled in that chamber. Ventricular flutter occurred on one occasion but was not recognized at the time. Paroxysmal auricular tachycardia and sinus tachycardia have occurred occasionally; rarely it has been deemed wise to terminate the procedure if they did not subside promptly. We have encountered other effects on the ventricular complexes, such as ST depressions and transient bundle branch block (23) but they have not deterred us from continuing.

On one occasion the catheter was passed into an artery in the antecubital

fossa by error. The vessel was then tied off and the radial pulse disappeared. Although the hand was slightly cool for a few hours, there was no other untoward effect. In retrospect it appeared that the radial artery had been tied at a point just distal to its origin from the brachial. In infants and children it is sometimes difficult to distinguish the artery from the vein, especially when the dissection has been deep. The most useful sign has been pulsation in the vessel.

Excessive bleeding around the catheter has occurred on rare occasions and is apt to be overlooked during fluoroscopy, when the lights are out. Phlebitis has occurred but has never been seriously distressing to the patient.

#### ANGIOCARDIOGRAPHY

Attempts were made to visualize the cardiac chambers and the great vessels as early as 1922. The usefulness of angiocardiology was enhanced in 1937 (24) by the introduction of a satisfactory contrast medium, namely Diodrast in 70% solution. This substance when injected into a peripheral vein not only opacified the right cardiac chambers and the afferent pulmonary vessels, but also permitted visualization of the pulmonary veins, the left chambers, the aorta, and its great vessels. Furthermore, the opacity of the Diodrast-containing blood after traversing the pulmonary circuit made it possible to delineate these structures not only in children but also in adults. With the application of this method to the study of the circulation in congenital cardiac patients (25), the necessity of multiple exposures during the opacification of the heart and its great vessels became apparent. In this hospital, cinematography with fluorescent screen was employed but limitations inherent in this method, namely low image brightness, slow film speed, and film grain combined to render the results unsatisfactory. Because of this, a wheel was devised (26) in which circumferentially situated cassettes were successively exposed after rotation into position before the patient. This slow and cumbersome device was replaced by an automatic cassette-changer (27) in which five lead-backed cassettes were arranged vertically on an inclined plane and, after exposure, caused to fall into a lead-protected compartment.

While this proved satisfactory, increased experience established the need for a greater number of exposures at brief intervals in conditions in which the circulation time is short. In fact, we have encountered cases of the tetralogy of Fallot in which Diodrast-containing blood could be demonstrated within the thorax during an interval not longer than three to four seconds. Attention has been directed to the possibility not only of incomplete diagnostic data but of erroneous interpretation in the absence of sufficient exposures during the transit of the opaque medium (28). Accordingly, in 1947, a new cassette-changer was built capable of utilizing up to 15 cassettes. To replace manual control of exposure, an electronic synchronizer was designed and built (29) in the Physics Laboratory of the Hospital. The synchronizer permits exposures to be made 1) manually, 2) by means of a variable-speed motor-driven "signal generator", and 3) by utilizing the electronically amplified R-wave of the action current of the heart in a trigger circuit. In each of these applications, the roentgen exposure

follows the "make" cycle of a relay. During the "break" cycle, this relay energizes a "cassette holding solenoid" thereby retracting a detent and allowing the exposed cassette to fall into a box via a guide chute. Immediately thereafter, the next cassette advances to the position vacated by the exposed cassette. This combination of synchronizer and cassette-changer is capable of exposing, discarding and replacing the 12 cassettes usually employed for an angiocardioqram in as short a time as 5-6 seconds. When the amplified R-wave is used to operate the exposure mechanism, delay circuits are available so that it is possible to predetermine the phase of the cardiac cycle in which each exposure will occur. During the angiocardioqram, a direct writing electrocardiogram is made which also records the exact time of occurrence of each exposure (Fig. 10). This is accomplished by feeding into the recorder a small voltage from the primary windings of the high voltage x-ray transformer.

#### E.C.G. DURING ANGIOCARDIOGRAPHY

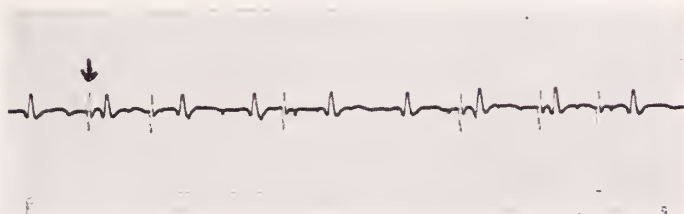


FIG. 10. Electrocardiogram taken during angiocardioqram, showing the first six exposures, taken at predetermined phases of the cardiac cycle. The remainder of the record has been omitted. The deflection caused by the feed-back from the first exposure is indicated by an arrow. The exposures are as follows: first exposure—first heart beat, 0.41 seconds after the R-wave; second exposure—second heart beat, 0.30 seconds after the R-wave; third exposure—fourth heart beat, 0.21 seconds after the R-wave; etc.

*Preparation of patients:* Preparation of adults for angiocardioqram alone consists of withholding the meal, usually lunch, immediately preceding the examination. Infants and children are anesthetized with ether outside the room in which the exposures are to be made. Deep surgical anesthesia is not required since the second plane has been found to suffice. Maintenance of hydration before and after anesthesia is of prime importance, especially in polycythemic individuals.

*Venous cannulation:* The importance of rapid injection (within one to two seconds) of the Diodrast in producing satisfactory visualization and in the avoidance of errors in interpretation (28) has been stressed. This requires the use of a twelve-gauge cannula<sup>11</sup> (24) and of a "Luer-lok" syringe with a twelve-gauge hole in its hub. To facilitate rapid injection, the Diodrast is warmed to body temperature just prior to its use. This serves to reduce its viscosity and to prevent crystallization within the syringe which may "freeze" the plunger.

Percutaneous introduction of such a large cannula is associated with a high percentage of failures to enter a vein. For this reason, we invariably expose the

<sup>11</sup> Becton-Dickinson, Catalogue number 485 LNR.



vein, usually in an antecubital fossa, and ligate the distal end of the exposed segment. After a small opening is cut in the vein, the cannula is introduced with the aid of a solid obturator. The tip of the latter is triangular in cross section, and all edges are smoothly rounded. The cannula is tied into the vein, the skin is sutured, and the hub of the cannula, to which a stopcock is permanently attached, is immobilized with flamed adhesive tape. A small amount (10 cc.) of normal saline is introduced into the cannula to replace the blood in it and to test the patency of the system. We have found it advantageous to introduce the cannula while the patient is in the x-ray department immediately before the procedure. When angiocardiography follows cardiac catheterization, it is a simple matter to withdraw the catheter and replace it with the cannula. The small skin incision is then sutured and the cannula immobilized as described above. Upon completion of angiocardiography, the cannula is withdrawn, and a pressure bandage is applied to prevent bleeding.

*Dosage:* Patients weighing 100 pounds or more receive 50 cc. of Diodrast. We have not used more than this quantity for a single injection. In children, one cc. of Diodrast per kilogram of weight is used, but 10 cc. constitutes the minimum dose.

*Selection of the position of the patient and the exposure rate:* All examinations are made with the patient in the erect position so that the diaphragm obscures the heart and lungs as little as possible. For the same reason, in unanesthetized patients, the injection is made at maximum inspiration. An immobilizing compression band applied around the thorax helps to maintain the patient in the position selected.

If right-to-left shunts or overriding of the aorta are suspected, exposures are made as rapidly as the system permits, namely twelve exposures in five to six seconds. In these conditions, the postero-anterior or left anterior oblique position may be used first. In suspected aortic lesions, the exposures are spaced to extend over an interval of eight to ten seconds and the most advantageous position of the patient is the extreme left anterior oblique. To differentiate mediastinal tumors from aneurysms, the postero-anterior position is preferred though not used invariably.

In all instances the exposed films are processed immediately and inspected. If it is then apparent that additional information is required a second injection is made with the patient in a different position. During the processing and inspection of the films, the patient has been resting in the recumbent position and is ready for the second injection, if the latter is indicated, by the time the initial films have been inspected and the cassettes reloaded.

The second injection consists of the same quantity of Diodrast as was used for the first. We do not administer more than two injections of Diodrast in the course of a single examination.

*Exposure factors:* High-speed screens are used behind a Lysholm grid. The latter is semi-permanently mounted behind the front panel of the cassette-changer. The target-film distance is sixty inches. A rotating anode tube of the heavy-duty type is used. The exposure is usually 1/60 of a second, occasionally

1/40 of a second, at 400 or 500 m.a. The kilovoltage used varies between 60 and 110 KVP. Short exposure time is regarded as the most important single factor in producing good definition in the films. Increasing the developing time helps to increase film density with these short exposures. More than average film density is favored because slight differences in contrast frequently permit identification of structures that otherwise might be obscured.

*Protection of personnel:* The direct beam is limited to the film area by a suitable cone at the x-ray tube. The person making the injection stands behind a leaded screen. The patient's arm is supported in the proper position, behind the screen, either by a sling hung over one end of the screen or by another person, who effects manual support. In examining anesthetized children an additional person, usually the anesthetist, wearing a leaded apron, is required to support the child's head.

*Diodrast reactions:* Just prior to the injection patients are informed of the discomfort which they will experience. This helps to reduce the reactions associated with surprise. Within seconds after the rapid injection of Diodrast in adults, intense warmth is experienced. Coughing frequently occurs. In other individuals, nausea and retching appear promptly though emesis is extremely rare. Most patients then experience throbbing headache and a transient desire to micturate. The pulse usually becomes rapid; occasionally a decrease in rate has been observed. Blood pressure apparently falls momentarily then returns to normal. In anesthetized dogs (30), arterial pressure falls precipitously to shock levels but within a few minutes returns to the original height.

It is our practice to place patients in the recumbant position as quickly as possible after the exposures have been completed. The cannula and vein are cleared of Diodrast by injecting 10 cc. of normal saline. Patients are assured that their discomfort is temporary. Either a physician or a nurse remains with the patient until the reaction has subsided. Ordinarily, in less than five minutes, patients are quite comfortable.

In anesthetized children no reactions have been noticed.

Because of the rather profound though brief effects of the injection on circulatory dynamics, we discourage these examinations in aged persons. However, several patients between the ages of 70 to 80 years have tolerated the procedure. In one case, following a single injection, a patient coughed intractably for about one hour but appeared perfectly well thereafter. Another patient, following a single injection, experienced profound nausea and retching for about two hours and then was able to travel to her home feeling perfectly well.

A 44 year old patient was allowed to walk to the lavatory approximately three minutes after the injection. He collapsed and was found to be in shock. Upon close questioning, he admitted experiencing vague precordial pain. Changes in the ST segment of the electrocardiogram were observed about two hours later but disappeared within 24 hours and all subsequent electrocardiograms were normal. After this, he submitted to excision of a mediastinal tumor and made an uneventful recovery.

A mongoloid infant, seven weeks of age, died immediately after angiocardio-

raphy. He had received two injections of Diodrast, but he had also been given a 50 cc. intravenous injection of normal saline before, between and after the Diodrast injections. Although death followed angiocardiology in this case, it seems probable that the large quantities of fluid administered also played a role in this fatality. In our series no other deaths have been associated with angiocardiology.

With the exception of infants and children, who are anesthetized for the procedure, patients are not hospitalized for angiocardiology alone. Ambulatory patients have been permitted to leave the Department after they have rested approximately 30 minutes following the last injection. Some members of the staff prefer to have patients hospitalized for angiocardiology.

Inflammatory reactions along the course of the injected vein are unusual if the Diodrast has been washed away promptly with 10 cc. of normal saline. Skin sutures are removed four to five days after the examination. Usually, Penicillin is administered as a prophylactic measure. We have performed subsequent angiocardiology at practically all intervals from one day to two years and we have found no evidence of sensitization to Diodrast.

*Sensitivity tests:* All patients receive one cc. of Diodrast intravenously as a test dose. If the angiocardiology is to follow cardiac catheterization, the test dose is injected through the cannula which has replaced the intracardiac catheter. If the patient is to have only an angiocardiology the test dose is injected before the vein is incised.

Occasionally, one of the subjective reactions that usually follow injection of the full dose is experienced immediately after this test. Formerly, such an occurrence was regarded as a contraindication to the administration of a larger dose of Diodrast. More recently, in six such instances, we have repeated the test dose after five minutes and when no reaction occurred we have injected 2 cc. and 5 cc. at five-minute intervals. In these six individuals the larger test doses were tolerated with no reaction and following angiocardiology with the full dose of Diodrast no unusual manifestations occurred.

In all instances, at least five minutes elapse before the test is considered negative.

Although all patients are tested in the manner described, we are of the belief that there is not currently available a reliable test for sensitivity to Diodrast and that at present no test can be relied upon to predict a patient's reaction to Diodrast as used in angiocardiology.

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## ELECTROCARDIOGRAPHIC ABNORMALITIES INDUCED BY CARDIAC CATHETERIZATION<sup>1</sup>

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AND FREDERICK H. KING, M.D.

The great importance of continuous electrocardiographic observation during cardiac catheterization has been repeatedly emphasized, since it is well known that a variety of abnormal rhythms and foci of irritability may be caused by contact of the catheter tip with the endocardium (1-7). Recognition of such aberrations and prompt withdrawal of the catheter from the excitable area are the chief safety factors in preventing the development of irreversible ventricular fibrillation.

Ventricular fibrillation, though still the major hazard of catheterization, is extremely rare. Many hundreds of procedures have been carried out, and only two instances of ventricular fibrillation with death have been reported. One was observed during arterial catheterization of the left ventricle (8) and the other during catheterization of the right ventricle in a case of Wolff-Parkinson-White syndrome (2), a syndrome noted for its propensity toward development of ectopic rhythms.

All cardiac catheterizations at this institution are controlled by observation of a direct-writing four-channel Cardiotron electrocardiograph, on which are recorded simultaneously two pressure pulses and two electrocardiograms. The leads used are either standard leads I, II, and III, or II and CF<sub>1</sub>. Though a continuous tracing is not recorded, the form of the complexes is readily ascertained with a little experience—even in total darkness—from the movement of the glowing stylus point.

This report deals with an analysis of these electrocardiographic tracings. Out of the total number of catheterizations done, 49 records were selected as suitable for analysis. Of these, 43 were from patients with congenital heart disease, 4 were normal, and there were 2 cases of rheumatic valvulitis. Of the patients with congenital heart disease, 18 were cyanotic.

*Findings:* Premature systoles (extrasystoles) were very common. Auricular premature contractions were noted in 7 cases (14 percent), and they occurred while the catheter was in either auricle. Nodal premature systoles were recorded in 11 cases (22 percent), and ventricular extrasystoles in 33 cases (67 percent). The ventricular extrasystoles occurred most commonly when the catheter was at the tricuspid orifice, or when it was either at the interventricular septum or being drawn from the pulmonary artery back into the outflow tract. These catheter-induced extrasystoles have been shown to arise in the right ventricle at the point of endocardial catheter contact, and consequently present a varying configuration in the standard leads, depending on the site of origin (6, 9). Some investigators have reported extrasystoles arising from both ventricles (2, 15).

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Supraventricular tachycardia was observed in 6 cases. Four of these could be identified as auricular tachycardia, and the origin of the other two was uncertain. They all began with the catheter in the auricle, were of a few minutes' duration, stopped spontaneously, and did not interfere with the progress of the catheterization other than momentarily.

Runs of 3 or more ventricular extrasystoles were considered ventricular tachycardia and were observed while the catheter was in the right ventricle in 12 cases (24 percent). There were 4 cases showing 5 consecutive beats or less, and 8 cases with more than five beats. The longest run was of 20 consecutive beats.

Occasionally patients became aware of a fluttery feeling in the chest, but otherwise no signs of lowered cardiac output were evident during the paroxysms. These runs ceased immediately or shortly after movement of the catheter from the excitable area.

TABLE I  
*Total number of cases—49*

	NO. OF CASES	PER CENT
Extrasystoles		
Auricular.....	7	14
Nodal.....	11	22
Ventricular.....	33	67
Tachycardia		
Supraventricular.....	6	12
Ventricular.....	12	24
Conduction Disturbances		
Partial A-V Block.....	1	2
Incomplete B.B.B.....	5	10
Complete B.B.B.....	3	6
S-T Segment and T Wave Changes.....	3	6

One episode of ventricular flutter with a rate of 240 per minute was encountered. This developed suddenly when the catheter tip was in the right ventricular outflow tract. The catheter was immediately withdrawn, and the flutter ceased spontaneously after 11 seconds. The tracing is shown in Figure 1. This patient was a male with an interatrial defect. His previous electrocardiogram had shown a pattern seen in right ventricular hypertrophy with an incomplete right bundle branch block. After an interval of rest, his condition seemed satisfactory, and an angiocardigram was performed on that same afternoon. No ill effects were noted.

There was only one other patient whose cardiac catheterization had to be discontinued because of an induced arrhythmia. This patient was a 19 year old white male with a heart murmur which was recognized at birth, an enlarged heart, and frequent episodes of paroxysmal tachycardia. His electrocardiogram was typical of a Wolff-Parkinson-White conduction. The clinical impression was pulmonic stenosis, but inasmuch as a diagnosis could not be definitely made upon

clinical grounds alone, catheterization was performed. One hour prior to catheterization, 0.75 Gm. of Pronestyl<sup>2</sup> was administered orally, anticipating possible ventricular tachycardia. As the catheter passed through the tricuspid valve a rapid tachycardia began, and the catheter was withdrawn into the axillary vein. The ventricular complexes were 0.14 sec. in duration and no P waves could be identified. This appeared to be a ventricular tachycardia and 0.4 gms. of Pronestyl were injected intravenously through the catheter. A transient return to sinus

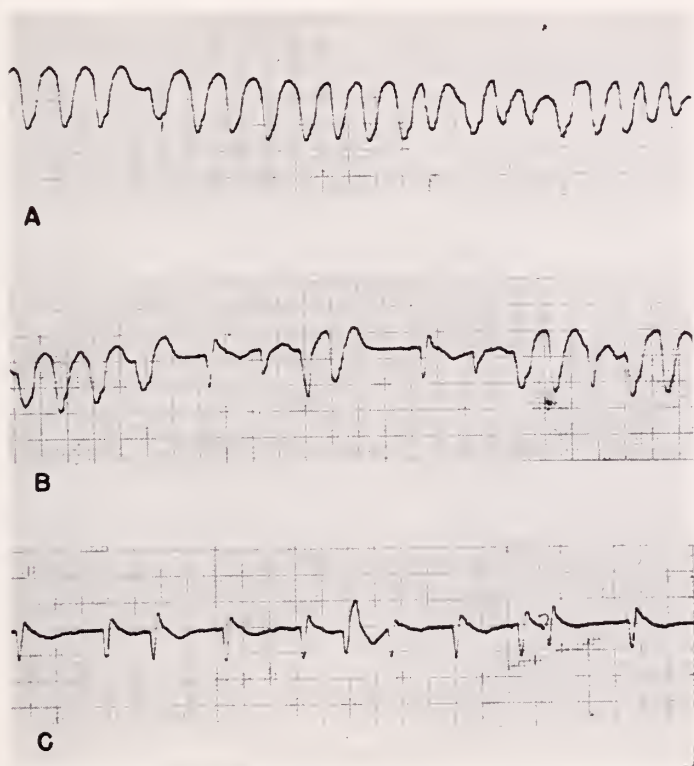


FIG. 1. *Ventricular Flutter.* A continuous electrocardiogram (lead  $CF_1$ ) which shows:  
A. Ventricular flutter of rate 240.

B. and C. Gradual transition back to normal rhythm after withdrawal of the catheter from the right ventricle.

rhythms was produced for 4 beats, the rhythm then changed to a nodal bradycardia, and finally the original tachycardia returned. A repeat intravenous injection of 0.4 gm. of Pronestyl produced no effect. It then became apparent that an auricular tachycardia with a conduction delay which resembled right bundle branch block was the mechanism of the tachycardia. Quinidine lactate, 0.65 Gm., was administered intravenously but had no effect. Eyeball pressure and carotid sinus pressure were likewise without effect. The auricular tachycardia continued for 2 hours longer, and 1.5 mg. of digoxin were administered intra-

<sup>2</sup> Procaine amide.



venously. Three hours later the heart returned to regular sinus rhythm with normal conduction. By the following morning, sinus rhythm with Wolff-Parkinson-White conduction had been restored. Electrocardiograms displaying some of the changes mentioned are shown in Figure 2. It would appear then that catheterization of patients with Wolff-Parkinson-White syndrome is more hazardous than of normals.

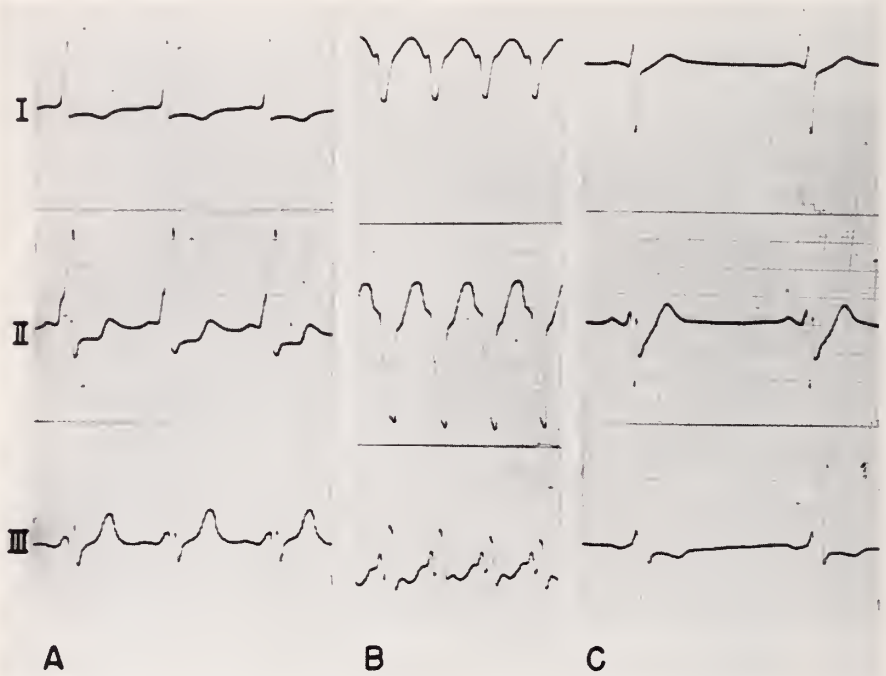


FIG. 2. Wolff-Parkinson-White Conduction.

A. Pre-catheterization electrocardiogram showing the short P-R interval, widened QRS complex and depressed ST segment characteristic of Wolff-Parkinson-White conduction.

B. Supraventricular Tachycardia, rate 150 which developed during catheterization. QRS width was 0.14 secs. and there was an apparent conduction delay in the right ventricle.

C. Transient return to sinus rhythm followed by normal auriculo-ventricular conduction. With conduction proceeding over normal pathways, marked right axis deviation was disclosed.

Though many aberrant rhythms were produced, some having a very frightening aspect, all subsided spontaneously. Most significantly, no irritable, discharging ventricular focus ever remained after removal of the catheter. This may be explained by the fact that human subjects, dying of causes not related to catheterization and autopsied shortly after catheterization, showed no endocardial bruises or hemorrhages which might serve as sites of origin of future ectopic rhythms (2, 10, 11, 12). This evidence from human seems to negate the significance of the observation that dogs do develop substantial lesions in auricles and ventricles even with very gentle catheter technique (12).

One instance of a second degree, 2:1 heart block was observed which persisted throughout the major portion of the catheterization. A return to normal conduction occurred at the time of completion of the procedure. During the return to normal conduction, typical Wenckebach periods of varying duration were observed.

S-T segment deviation and T wave changes were seen in only 3 cases. Depressions of the S-T segment of 1 mm. and 3 mm. respectively were observed

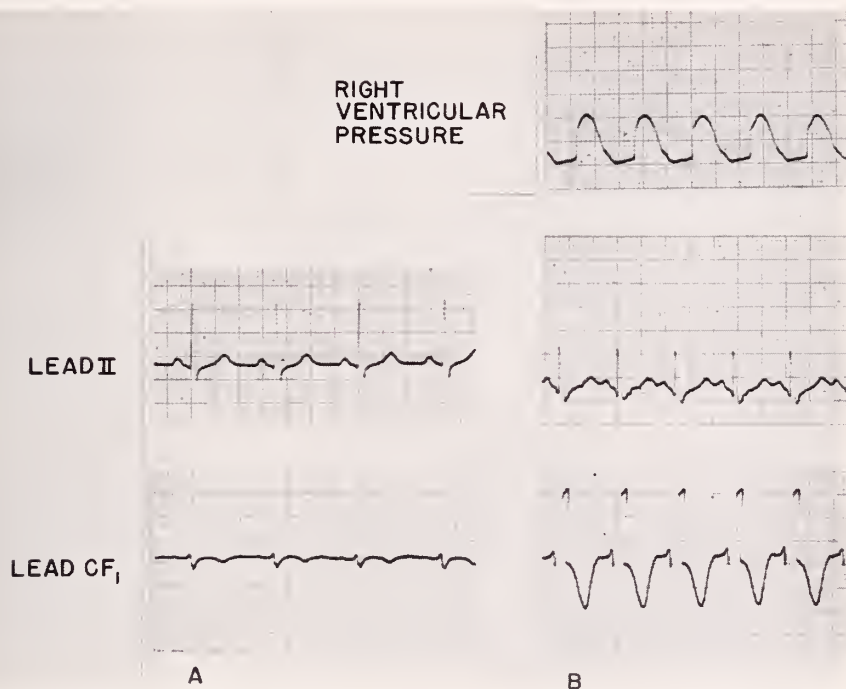


FIG. 3. *Right Bundle Branch Block.*

A. Normal electrocardiogram (leads II and CF<sub>1</sub>) taken immediately before catheterization.

B. Simultaneous electrocardiogram and pressure tracing taken while catheter is in right ventricle. The QRS width has increased from 0.08 to 0.13 sec., a broad S has appeared in lead II, and a tall wide R<sup>1</sup> in lead CF<sub>1</sub>.

during and following two cases of supraventricular tachycardia with rates of 140 and 150 beats per minute. Flattening of an upright T wave was seen following a ventricular tachycardia of 13 beats. These changes are not necessarily due to coronary insufficiency, but can be seen in normals with sinus tachycardia. The infrequency of S-T segment and T wave changes is explained partly by the observation that the currents of injury frequently recorded by endocardial leads as S-T segment elevations do not manifest themselves in the precordial or limb leads (6), where they would be recorded as S-T segment depressions. Moreover, though many of the patients were cyanotic and became more so during the catheterization, none showed evidence of coronary insufficiency.

This is in accord with the observation that during anoxemia tests, the cyanotic children do not develop S-T segment depressions (13). They seem to be adapted to severe anoxemia (13).

Eight patients (16 percent) developed widening of the QRS complex. Two of these showed an increase of 0.02 sec., three of 0.03 sec., one of 0.04 sec., and two of 0.05 sec. In five of these cases, lead CFI or standard lead I were available and permitted the probable assignment of the intraventricular conduction disturbance to the right ventricle. This conclusion was based on the development of a widened, slurred S wave in Lead I or a wide, tall, notched R or R-prime

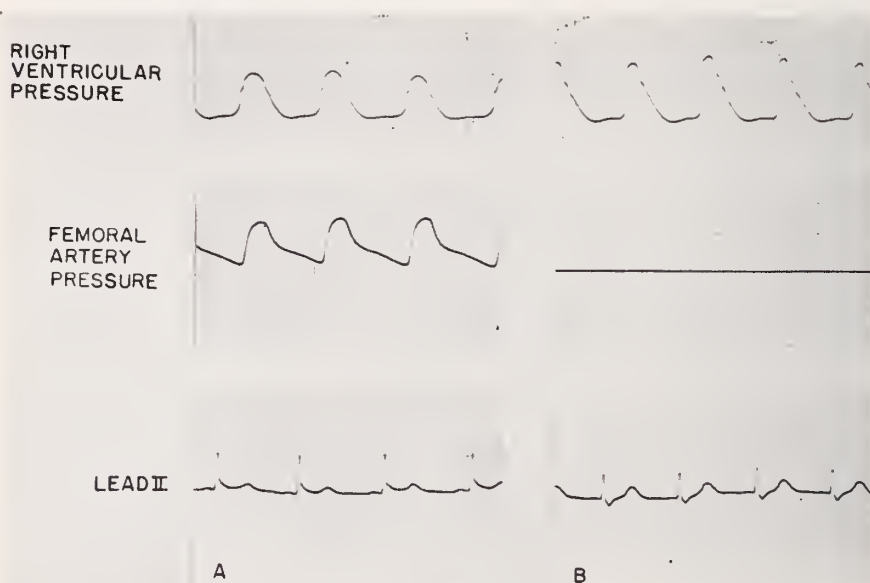


FIG. 4. *Right Bundle Branch Block.*

A. Simultaneous tracing of right ventricular and brachial artery pressure and lead II. The time interval from the onset of QRS to the rise in intraventricular pressure is 0.135 sec. Right ventricular pressure equals 18/0 mm. Hg.

B. Tracing taken after the development of right bundle branch block. The QRS width has increased from 0.07 to 0.11 sec., a wide S has appeared in lead II, and the time interval from the onset of QRS to the rise in intraventricular pressure is 0.16 seconds. Right ventricular pressure equals 20/0 mm. Hg.

wave in CF<sub>1</sub> with a deeply inverted T wave. In the other 3 cases only Leads II and III were available. Though they, too, were probably conduction disturbances of the right ventricle, no definite statement can be made, other than that widening of the QRS was present. In 3 cases, the QRS exceeded 0.12 sec., and these were therefore considered complete right bundle branch block. The remaining 5 cases were considered incomplete or local blocks.

These conductive disturbances developed with the catheter in the right ventricle in 6 cases, and in the pulmonary artery in 2 cases. Both of the latter were complete blocks but only one of the former was complete. Three were quite transient, lasting 3, 10, and 15 minutes respectively, and five were still

present at the end of the procedure. Of these five, three had follow-up electrocardiograms one and two days later, which showed complete reversion to normal. Angiocardiograms were done following the catheterizations and no untoward effects were observed. There was no correlation with the type of congenital lesion or with previous electrocardiograms. Conduction disturbances of this type have been described before, and do not appear to be permanent or significant (2, 3, 6).

Right ventricular pressures were obtained in two of these cases during periods of both normal and prolonged conduction. The first patient was a 15 months old child with tetralogy of Fallot. The QRS width increased from 0.06 sec. to 0.08 sec. The average interval from the onset of the QRS in Lead I to the onset of the abrupt rise in right ventricular pressure did not change significantly. It was 0.105<sup>3</sup> sec. with normal conduction and 0.115\* sec. with the prolonged conduction time.

The second patient was a 34 year old female with idiopathic dilatation of the pulmonary artery. Her QRS changed from 0.07 to 0.11 sec. The average QRS-right ventricular systolic interval changed from 0.135\* sec. to 0.16\* sec. as shown in Figure 4. This delay in the onset of mechanical systole of the right ventricle indicates a late excitation of a major portion of that chamber. This is similar to the observation of Coblenz, et al., in two cases of right bundle branch block induced by quinidine (14).

#### SUMMARY

A large number of auricular, nodal and multifocal extrasystoles, 6 supraventricular tachycardias, 12 ventricular tachycardias and one case of ventricular flutter were observed during cardiac catheterization. The supraventricular tachycardias appeared to be innocuous and ceased spontaneously, except in one patient with Wolff-Parkinson-White syndrome where the tachycardia persisted for 5 hours. When the catheter was promptly removed from an excitable area, ventricular extrasystoles quickly ceased and no persistently discharging ectopic ventricular focus remained. One case of partial A-V block was observed. Conduction disturbances of the right ventricle were not uncommon, and reverted to normal after a variable period of time. One case of right bundle branch block, showing a prolongation of the interval between the onset of ventricular excitation and the right ventricular mechanical response has been reported.

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<sup>3</sup> Uncorrected for lag of transmission of pressure pulses through catheter and recording system.



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## FURTHER EXPERIENCES WITH MICROPLETHYSMOGRAPHY IN THE STUDY OF CONGENITAL HEART DISEASE\*

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The contour of the peripheral volume pulse wave is partially determined by the mechanics of left ventricular ejection and by the manner in which the post-systolic column of blood is transferred through the aorta. Certain diseases of the heart despite their gravity fail to produce any demonstrable alteration in peripheral blood flow. This stems from the fact that influences which could conceivably affect the volume distribution of blood operate centrally within the chambers of the heart. Other cardiac defects, for example stenosis or insufficiency of the aortic valves, lead to gross changes in peripheral hemodynamics, the specific characteristics of which permit their recognition by physical examination. There are other cardiovascular diseases which are also capable of inducing specific derangements in peripheral blood flow patterns, but their detection ordinarily requires more complex analytical methods. Recently we have described the application of one such method, namely microplethysmography, to the diagnosis of certain of these latter disorders (1). The present report details further experiences with this technique and summarizes the present viewpoint on the position of microplethysmography in the integrative study of congenital heart disease.

The physical characteristics of the microplethysmograph and the principles of microplethysmographic recording have been described elsewhere (2, 3). The details of the composite volume changes which comprise the microplethysmogram have been described also. Nevertheless, it is germane to reemphasize certain features. The microplethysmogram is a graphic time curve of the digital volume fluctuations. While these include continuous alterations in both intravascular and extravascular fluid compartments, for practical purposes they are considered to represent a summation of constant phasic and aphasie changes in digital blood volume. The magnitude and the characteristics of these changes depend primarily upon ventricular systole, the circulating blood volume, digital volume, the anatomical status of the heart and blood vessels, and also upon vasomotor tone. Factors such as local reflexes and digital arteriovenous shunts, while capable of modifying a tracing considerably, are unimportant in the microplethysmographic study of congenital heart disease.

The basis for the plethysmographic diagnosis of cardiovascular anomalies entails the proper analysis of the volume pulse wave. This is a positive biphasic pulsation characterized normally by an abrupt almost vertical upward deflection, the systolic limb, and by a more oblique downward deflection, the diastolic limb. The former is the result of a rapid increase in digital blood volume after the isometric phase of ventricular contraction. The latter represents the progressive decrease in aeral volume resulting from the continuous venous runoff during the phase of ventricular filling. The difference in the gradient of the respective slopes

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est deflection per c.c. of digit occurs in the finger. Phasic volume changes in response to respiration are also more pronounced in the upper extremity. On the other hand the more pronounced alpha wave activity noted so frequently in the toetip as compared with the fingertip is attributable to the differences in vaso-motor tone which exist normally in both sets of extremities.

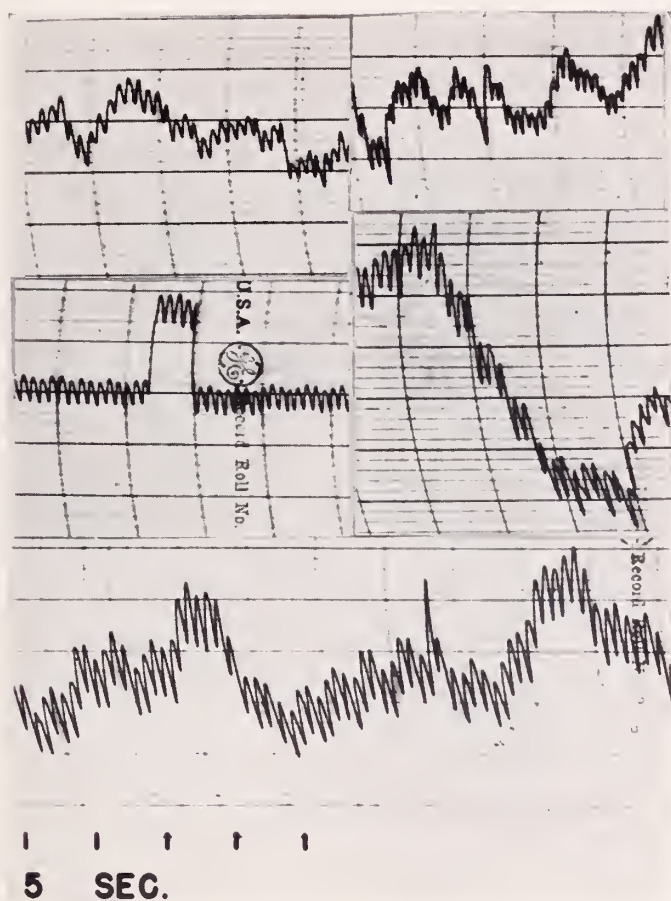


FIG. 2. Digital microplethysmograms in five proven instances of patent ductus arteriosus. Note the rounded apex, the symmetrical limbs, and the absent dicrotic notch.

In the interval since the previous report, a microplethysmographic diagnosis of patent ductus arteriosus was made in an additional forty-six patients. The microplethysmographic criteria which reflect the presence of patency, namely the appearance of a flat, obtuse or rounded apex, the absence of a distinct dicrotic notch, the loss of the normal difference in the gradient between the systolic and diastolic limbs, and the variations in volume pulse amplitude, were present either in part or in their entirety in all these subjects. Confirmation of the microplethysmographic diagnosis was obtained in the entire group either by cardiac catheterization, by angiocardiography, or by thoracotomy (fig. 2).



Ten additional patients suffering from persistent cyanosis underwent the Blalock-Taussig operation in this same period. Six of these patients manifested a continuous bruit postoperatively. In these patients the characteristic plethysmographic changes associated with patent ductus were noted. Despite the absence of a typical murmur after operation, increased exercise tolerance and  $O_2$  saturation, and a decline in the red blood cell count and in the concentration of hemoglobin were observed in three of the remaining four patients. This would suggest the existence of a functioning arteriovenous communication. Microplethysmograms verified the existence of such a shunt in two of these patients.

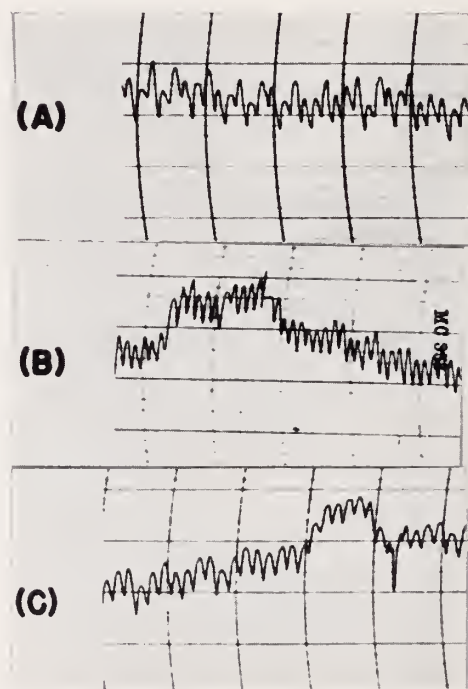


FIG. 3. Digital microplethysmograms, (A) aortic septal defect, (B) dissecting aneurysm of sinus of valsalva, (C) aortic aneurysm. Note that the alterations in the volume pulse wave contour are identical to those noted in patent ductus.

The basis for the normal plethysmogram in the remaining patient who exhibited improvement is conjectural. Conceivably it could result from spontaneous thrombosis, in the artificial ductus, although what appears more likely is that clinical improvement resulted from temporary reduction in the severity of the polycythemia following blood loss during the course of the operation.

It was mentioned previously that certain cardiovascular abnormalities such as systemic arteriovenous aneurysm and aortic aneurysm may be indistinguishable plethysmographically from patent ductus arteriosus (1). During the course of subsequent investigations, the pathognomonic digital pulse volume changes of patency were noted in two additional patients. In one, the history and localization of the murmur indicated that the altered plethysmogram was the result of an

aneurysm of the sinus of Valsalva which had ruptured into the right ventricle. The other patient was subjected to exploratory thoracotomy. Operation disclosed that the plethysmographic abnormalities were the result of an aortic septal defect (fig. 3). It is apparent that the fundamental alterations in peripheral circulatory hemodynamics resulting from a systemic arteriovenous aneurysm, patent ductus arteriosus, an aortic septal defect, and an aneurysm of the sinus of Valsalva which has ruptured into the cavity of the right ventricle, are similar. The arteriovenous shunt in all these cardiovascular disorders operating as a surge tank ("Windkessel") minimizes comparatively rapid and small volume

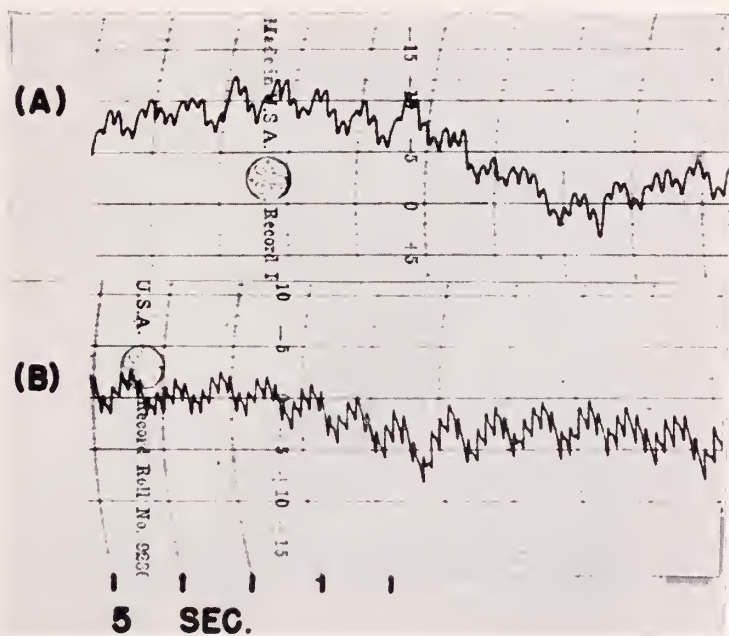


FIG. 4. Digital microplethysmograms before (A), and after (B), ligation of a patent ductus. Note that following ligation the volume pulse wave contour returns to normal.  
 Fingertip microplethysmogram  
 Volume of Finger—5 cc  
 Pulse amplitude—4 mm.  
 Toetip microplethysmogram  
 Volume of Toe—18 cc  
 Pulse amplitude—2 mm.

changes such as the dicrotic notch. The mechanism has been compared to the electromechanical equivalent of a by-pass condenser, acting as a low-pass filter. This explanation accounts for the loss in the slope gradient between the component limbs and for the presence of rounding of the apex of the volume pulse wave.

In the great majority of patients a normal plethysmogram was obtained within the first two weeks following surgical closure of the ductus (fig. 4). A few patients continued to manifest alterations for a variable period postoperatively although not exceeding one year. Examination of a group of six patients who had undergone surgical ligation prior to 1946 when the plethysmographic studies were first instituted have failed to reveal any defects in the digital volume pulse wave.

It was previously reported that the plethysmographic patterns from the fingers and toes exhibit diagnostic alterations in the presence of coarctation of the aorta. The statement was made that occurrence of this congenital anomaly induced a reversal in normal volume relationships. This was evidenced by the fact that the amplitude of both the volume pulse and alpha waves were either less than or were no greater than their counterparts in the fingers (1). In the period since this report we have had the opportunity to study nine additional patients with coarctation of the aorta. This additional experience has demonstrated the need for modifying certain of the original microplethysmographic criteria. We have found that the characteristic plethysmographic defect in coarctation is a bilateral

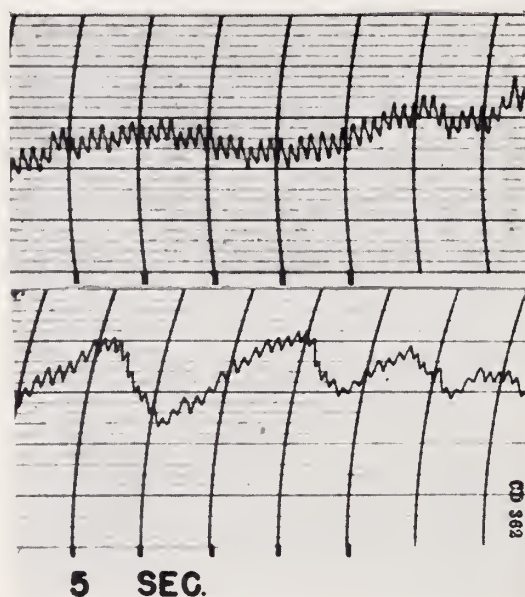


FIG. 5. Fingertip and toetip microplethysmograms in coarctation of the aorta. Note the reversal in finger and toe uncorrected volume pulse wave relationship. Well developed alpha waves are present in the toetip tracing.

and relatively equal reversal in the normal pulse amplitude relationships. However contrary to previous observations, these studies revealed a pronounced dissociation between the volume pulsations and the alpha waves in eight out of the nine patients. This was manifested by absent or minimal alpha wave activity in the upper extremities and frequent high amplitude alpha waves in the lower extremities (fig. 5). The significance of these findings will be discussed at length in a separate publication.

#### SUMMARY

At present microplethysmography serves as a useful and valuable diagnostic tool for the evaluation of certain congenital cardiac defects. Tracings are now obtained routinely in all suspected instances of both congenital or acquired

systemic extracardiac arteriovenous communication and in coarctation of the aorta. The value of this technique as an aid in the diagnosis of certain other congenital cardiac defects such as patency of the auricular or ventricular septum is speculative.

Ease of recording and simplicity of interpretation make the method especially adaptable for those patients in whom typical physical signs are not observed or in whom certain contraindications such as age, drug idiosyncrasy, etc., make the more formidable diagnostic procedures inadvisable, if not impossible.

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## AORTIC SEPTAL DEFECT SIMULATING PATENT DUCTUS ARTERIOSUS\*

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There are several congenital cardiovascular anomalies which may simulate clinically patent ductus arteriosus. These include aneurysm of a sinus of Valsalva communicating with the right auricle or ventricle (1), ventricular septal defect (2), arteriovenous aneurysm of the pulmonary artery (3), and aortic septal defect (4, 5) leading to a communication between the aorta and pulmonary artery at a point above the aortic sinuses. Some of these may be differentiated from patent ductus arteriosus by the findings at catheterization and angiocardiography. Thus in a case which clinically simulated patent ductus arteriosus, Moran and Burchell (2) were able to demonstrate the presence of a ventricular septal defect by catheterization. Patent ductus was excluded by exploratory thoracotomy. In this hospital we have succeeded in demonstrating by angiocardiography the presence of an aneurysm of the sinus of Valsalva intruding into the right auricle (6). However in this instance the clinical manifestations did not simulate patent ductus. Pulmonary arteriovenous communications are not infrequently demonstrable angiographically.

The anomaly which most closely simulates patent ductus arteriosus, and is, therefore, difficult to differentiate from it, is aortic septal defect. This is understandable for the communication in both anomalies lies between the aorta and the pulmonary artery. They differ only in that the shunt in patent ductus is via a short vascular conduit while in aortic septal defect the shunt is directly through a defect in the wall between the two vessels just above their origins. So nearly identical are the findings that the exclusion, it seems to us, of a patent ductus by exploration in a case in which the clinical and laboratory findings are characteristic of uncomplicated patent ductus renders it almost a certainty that the anomaly is an aortic septal defect. Such an instance is demonstrated in the following report:

### CASE REPORT

A boy aged 11 years who had been followed as a congenital cardiac at another clinic since the age of 2½ months was admitted to the hospital for closure of a patent ductus arteriosus. His development since birth was slow. At the age of 2½ months he had a convulsion; 6 months before entering the hospital he had a "fainting spell" while playing in the street. There was a vague and unconfirmed history of occasional cyanosis but exercise tolerance was apparently good, allowing him to keep up with his friends in all their activities.

One year before admission, and again just before entering the hospital, the child's mother was advised to have her child operated upon for closure of a patent ductus. She brought the boy to the Congenital Cardiac Clinic of the Mount Sinai Hospital, indicating her desire to have the operation performed, and he was admitted to the Pediatric Service.

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*Examination.* The boy was poorly nourished and poorly developed with a prominent bony chest. There was no cyanosis. The lungs were clear. Examination of the heart disclosed the point of maximal impulse to be outside the midclavicular line but difficult to localize due to the strong impulse. The heart sounds were prominent but muffled by a very coarse, loud systolic murmur heard throughout the precordium and transmitted all over the chest. There was a diastolic component giving a machinery-like sound which was heard best at the 2nd intercostal space to the left of the sternal border. There was a systolic thrill over

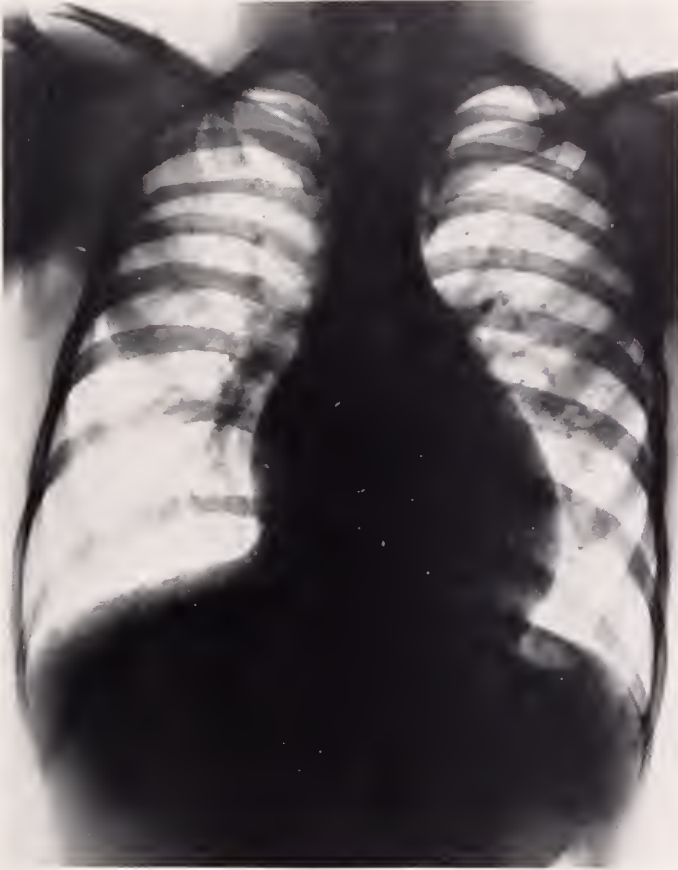


FIG. 1. Conventional film shows increase in the transverse diameter of the heart, prominence of the pulmonary artery segment and of the upper right cardiac contour. The aortic knob is small. The pulmonary vascular markings are slightly increased.

the precordium with a smaller diastolic thrill. The pulmonic second sound was louder than the aortic. The heart rate was 120 per minute. The blood pressure at rest was 102, systolic, and 58, diastolic. After exercise, it was 94, systolic, and 38, diastolic. The femoral pulses were palpable and equal.

Radiographic and fluoroscopic examination of the chest (fig. 1) showed moderate increase in the transverse diameter of the heart with prominence of the pulmonary artery segment of the left cardiac contour. The hilar vessels were widened but showed no hilar dance. Prominence of the upper right cardiac contour in the postero-anterior projection and of the region of the right auricular appendage in the left anterior oblique view suggested the

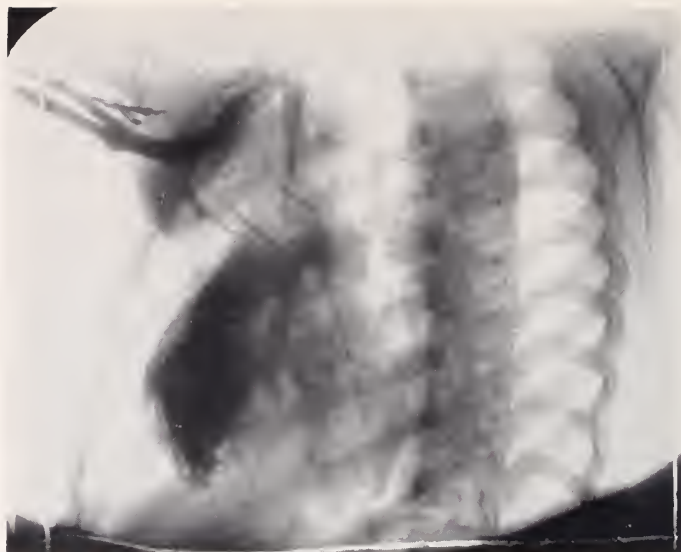


FIG. 2. Angiocardiogram made in the left anterior oblique projection shows diodrast-containing blood in the superior vena cava, right atrium and right ventricle. The slightly dilated pulmonary artery is densely opacified as far as the region of its bifurcation, beyond which the right and left pulmonary arteries are faintly visualized.

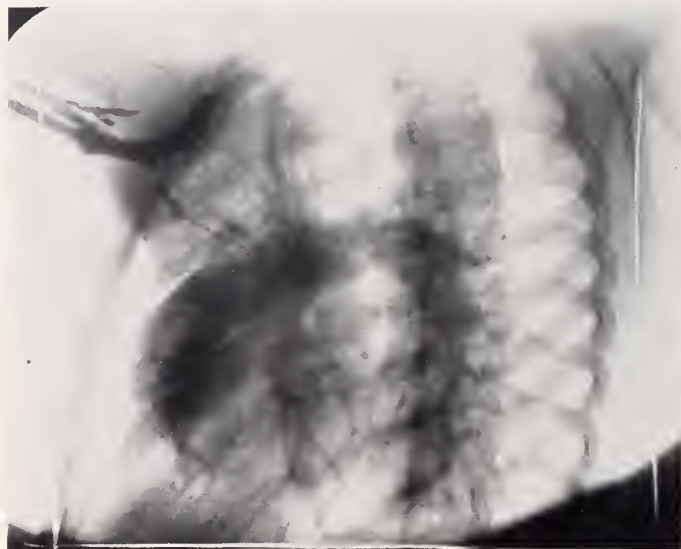


FIG. 3. This was exposed about one second after figure 2. The right ventricle is faintly outlined. The opacification of the pulmonary arteries is maximal at this time. The discrepancy in the densities of the pulmonary artery and its right and left branches is striking.

possibility of right auricular enlargement. The aortic knob was normally situated but small. The barium-filled esophagus was not displaced. There was no evidence of any pulmonary infiltration or anomalous pulmonary vessels.

The electrocardiogram showed no definite axis deviation. There was regular sinus rhythm (fig. 4).

The phonocardiogram showed at the pulmonic area a high amplitude, high frequency, crescendo systolic murmur which was continuous with a decrescendo diastolic murmur. The pulmonic second sound was obliterated by the murmur (fig. 5).

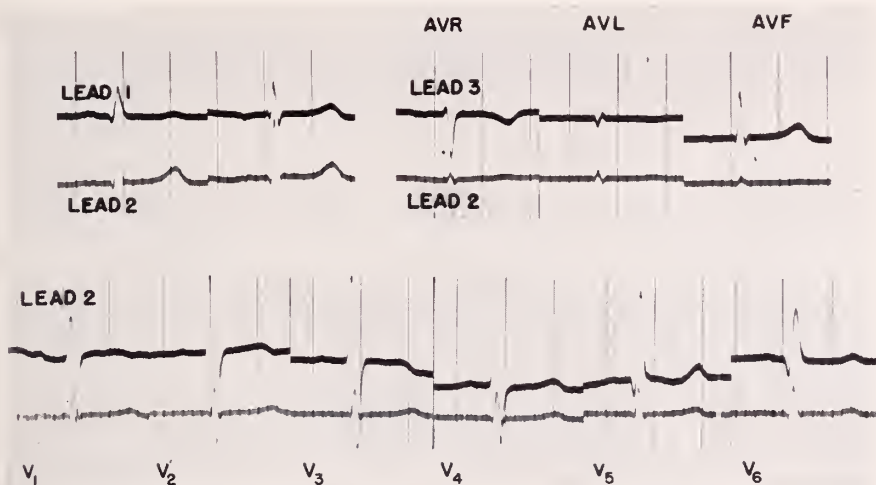


FIG. 4. Electrocardiogram showing regular sinus rhythm. There is no definite axis deviation.

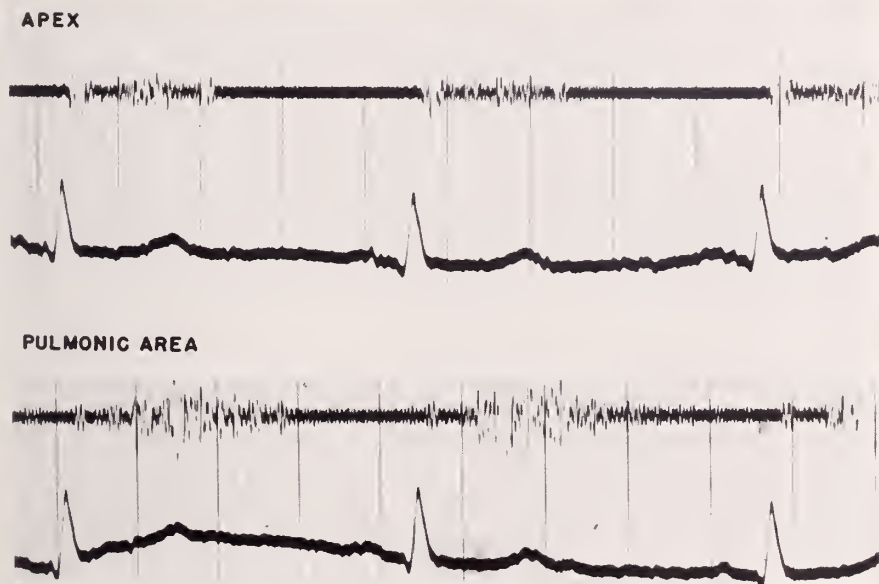


FIG. 5. Phonocardiogram showing at the pulmonic area a high amplitude, high frequency, crescendo systolic murmur with a decrescendo diastolic murmur.

The microplethysmogram of one of the fingers exhibited the typical volume pulse contour alterations associated with an extra-cardiac arterio-venous communication.

Although the clinical findings and the results of laboratory procedures thus far performed



were almost pathognomonic of patent ductus arteriosus, the possibility of an associated lesion was considered because of the vague suggestion of atrial enlargement on roentgenographic examination. For this reason it was decided to pursue the investigation further with cardiac catheterization and angiocardiography.

During cardiac catheterization no abnormal communications were demonstrated by the exploring catheter. The findings were as follows:

LOCATION	OXYGEN CONTENT	PRESSURE
	vols. %	mm. Hg.
Superior vena cava	10.0	-1 mean pressure
Right atrium	11.6	-1 mean pressure
Right ventricle (tricuspid)	12.0	35/0
Right ventricle (outflow)	12.0	35/0
Main pulmonary artery (near left PA)	13.5	14/7
Main pulmonary artery	14.3	13/5
Right pulmonary artery	13.7	10 mean pressure
Left pulmonary artery	13.3	18/9
Femoral artery	16.5	
Oxygen capacity	16.9	
Per cent saturation	99%	

An oximeter study during standard exercise failed to demonstrate any significant arterial unsaturation.

An angiocardiogram taken in the left anterior oblique position showed the superior vena cava, the right atrium, including its appendage, and the right ventricle to be normal in size. The main pulmonary artery appeared somewhat large. All of the structures distal to the bifurcation of the main pulmonary artery were insufficiently opacified to warrant a diagnostic statement despite the fact that the quantity and speed of injection of the contrast medium were adequate. This was believed to be an indication of very rapid dilution of the diodrast-containing blood by arterial blood entering the pulmonary artery through a very large patent ductus arteriosus (figs. 2 and 3).

In summary, the features leading to a diagnosis of patent ductus arteriosus were: 1. Systolic and diastolic murmur over the pulmonic area; 2. Wide pulse pressure with decrease in diastolic pressure on exercise; 3. Elevated blood oxygen content in the pulmonary artery; 4. Typical volume pulse contour alterations on micropneumogram. The decreased systolic pressure within the pulmonary artery with slight elevation of right ventricular pressure is assumed to indicate mild pulmonic stenosis.

Because of these findings the patient was operated upon for closure of the suspected ductus arteriosus by Dr. Arthur Touroff. At operation the heart was found to be enlarged. A thrill was palpated in and around the pulmonary artery. A patent ductus was not found. The ligamentum arteriosum was identified in the usual position between the aorta and the pulmonary artery. This structure was divided without clamps and was found to be an elongated fibrous cord. Palpation of the pulmonary artery revealed a continuous thrill. There was a faint thrill in the aorta. This vessel was enlarged to about  $1\frac{1}{2}$  times the normal size but the wall was of normal thickness. Pressure on the ascending aorta did not obliterate the thrill in the pulmonary artery. It was assumed that the congenital defect was proximal to the point of pressure, viz. at the base of the heart. No attempt was made at this time to undertake repair of the fistulous communication.

Following operation the patient made an uneventful recovery and was discharged.

#### COMMENT

Although the septal defect was not physically demonstrated, the evidence of a large aortic-pulmonary artery shunt together with the exclusion of a patent

ductus at exploratory operation makes it almost certain that an aortic septal defect exists. This case illustrates the extreme difficulty in making the differential diagnosis. Because of its rarity the possibility is not often considered. Except for the superficial character of the murmurs and thrill in aortic septal defect (1) no really distinguishing clinical features exist. The association of superficial murmurs and thrill with evidence at catheterization of a large shunt may lead to the suspicion of the diagnosis.

This case illustrates a feature of the angiocardigram which may, in addition to the aforementioned, lead to suspicion of the diagnosis preoperatively. This consists of the failure to visualize well the pulmonary artery branches distal to the bifurcation of this artery because of the dilution of the diodrast-containing blood in the pulmonary artery by the large amount of blood shunted into it from the aorta. This is less likely to occur with the usual patent ductus, possibly because the shunt is ordinarily smaller than in aortic septal defect. Dodds and Hoyle (5) surmised that in aortic septal defect "the injection of contrast media by the basilic vein is unlikely to provide conclusive evidence regarding the exact site of the aortic pulmonary leak because dilution in the pulmonary artery by the aortic blood would make radiographic interpretation difficult". In this prediction they were correct. Yet it is precisely this failure to visualize adequately the distal portion of the pulmonary artery which may indicate the presence of a large shunt and give rise to the suspicion of an aortic septal defect rather than patent ductus.

The possibility exists that retrograde angiocardiology would demonstrate the aortic septal defect but this was not undertaken.

The systolic pressure in the pulmonary artery was distinctly lower than in the right ventricle where the pressure was only slightly elevated. This suggests the presence of mild pulmonary stenosis. The association of pulmonary stenosis and aortic septal defect has been mentioned casually by Dexter (7) and would appear to be a rather frequently associated anomaly.

The possibility of the repair of the fistula by using two Potts clamps exists. It is our intention to recall this patient and have a reparative operation performed if feasible.

#### SUMMARY

1. A case of aortic septal defect possibly associated with mild pulmonary stenosis and simulating patent ductus arteriosus is described.

2. The differential diagnosis from patent ductus arteriosus may not be possible. However, the presence of superficial to and-fro murmurs and a thrill, together with clinical and laboratory evidences of a large shunt between the aorta and pulmonary artery are features favoring aortic septal defect rather than patent ductus arteriosus.

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## ISOLATED INTERVENTRICULAR SEPTAL DEFECT WITH DILATATION OF THE PULMONARY ARTERY, AN ENTITY<sup>1</sup>

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In 1879, Roger (1) described congenital isolated interventricular septal defect. The lack of symptoms, the mesocardial, harsh, holosystolic murmur, the minimal cardiac enlargement, and the good prognosis were characteristic. By anatomical and clinical studies, Abbott (2), Brown (3), and Taussig (4) confirmed these original observations. Dilatation of the pulmonary artery and its branches was considered to be exceptional. In a previous paper, one of us (5) reported the clinical and postmortem findings in isolated interventricular septal defect with dilatation of the pulmonary artery. The lesion was considered a clinical entity and was included in the differential diagnosis of congenital lesions associated with radiographic prominence of the pulmonary artery segment. These include interatrial septal defect, patent ductus arteriosus, Eisenmenger's complex, idiopathic dilatation of the pulmonary artery, and isolated pulmonic stenosis with post-stenotic dilatation.

The case to be presented illustrates the clinical features and the procedures necessary for the establishment of the diagnosis.

### CASE REPORT

*History.* M. C., a 4½ year old boy, was admitted to the Mount Sinai Hospital on March 23, 1950, for investigation of his congenital heart lesion. The patient was born at term following a normal pregnancy and delivery. When the patient was a few weeks of age, a doctor told the parents that the child had a heart murmur. There had never been any cyanosis, shortness of breath, or limitation of activity. The patient had always had a poor appetite but otherwise development had been normal.

*Examination.* The boy was well developed, well nourished, and did not appear ill. The pulse rate was 100 per minute, respirations were 24 per minute, and the blood pressure was 105 systolic and 70 diastolic. The weight was 33½ pounds. There was weakness of the right external rectus muscle. Several teeth were carious and the tonsils were moderately enlarged. The neck veins were not distended and there were no abnormal cervical pulsations. There was a slight depression of the sternum and a moderate bulging of the left side of the chest. The lungs were clear to percussion and auscultation. The apical impulse of the heart was at the fifth intercostal space 1 cm. lateral to the mid-clavicular line. A systolic thrill was palpable along the left sternal border; it was maximal at the fifth intercostal space and over the region of the xiphoid. The thrill was also palpable over the epigastrium and at the region of the apex impulse. Sinus arrhythmia was present. P2 was louder than A2. A very loud (grade 5), harsh, medium-pitched systolic murmur was heard maximally over the fourth

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and fifth intercostal spaces at the left sternal border. The murmur was well transmitted over the entire precordium and the epigastrium; it was also transmitted to the right side of the chest, the axillae, the neck, and to both sides of the posterior thorax. The femoral and radial pulses were of good quality. The liver and spleen were not palpable. There was no clubbing of the fingers or toes. There was no cyanosis or edema.

Fluoroscopy in the posterior-anterior position revealed that the heart was enlarged predominantly to the left. The pulmonary artery segment was prominent and the pulmonary artery branches were large, but there were no abnormal pulsations. In the right anterior oblique position the pulmonary artery segment was enlarged and the anterior cardiac border encroached upon the retrosternal space. In the left anterior oblique position there was no definite abnormality. There was an anterior displacement of the barium-filled esophagus above the aortic knob in the right oblique view.

Laboratory examination showed a red blood cell count of 4.3 million per cu. mm. and a hemoglobin of 12.5 grams per 100 cc. The white blood cell count was 11,500 with 77% neutrophils. The urinalysis was normal.

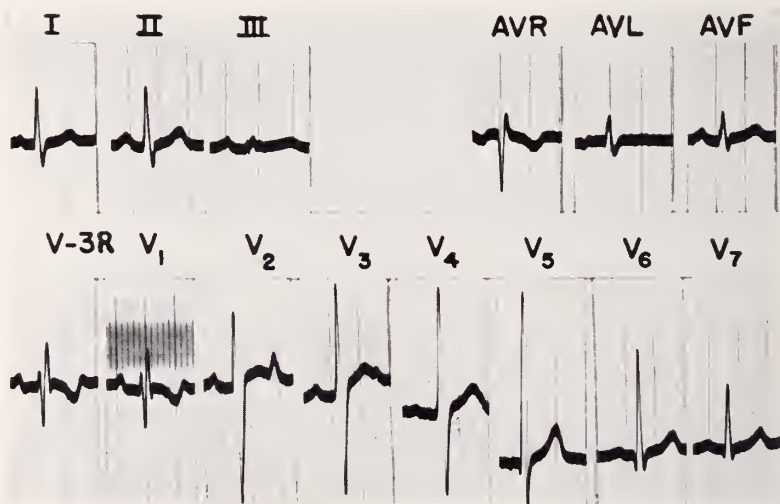


FIG. 1. Electrocardiogram: There is an R-R' pattern in V3R and V1 which indicates a mild conduction delay in the right ventricle.

The electrocardiogram (fig. 1) showed a sinus arrhythmia with a rate of 100 per minute. The axis was normal. The QRS measured 0.08 seconds. P1 was notched. A small S was present in lead I. The unipolar limb leads showed an intermediate position. In AVR there was a deep Q and a late R wave. In AVL there was a diphasic P wave and the T was flat. The unipolar chest leads showed an rSR' pattern in V3R and V1. The intrinsicoid deflection in V1 occurred 0.06 seconds after the onset of the QRS. There was a qRs in V5 and V6. These findings suggested that there might be a mild conduction delay in the right ventricle.

The phonocardiogram (fig. 2) showed a high amplitude and high and low frequency murmur which occupied the entire period of systole in tracings taken over all areas of the precordium. The murmur was recorded with maximal intensity over the xiphoid and the fourth intercostal space at the left sternal border; in these areas the murmur was of higher amplitude than the heart sounds.

The microplethysmogram showed no evidence of an extra-cardiac arterio-venous communication.

A chest x-ray (fig. 3a) revealed that the heart was enlarged especially to the left. The pulmonary artery segment was prominent. The pulmonary hilar vessels were prominent,

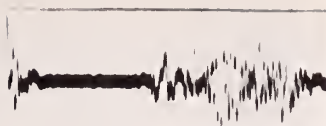
**XIPHOID****4TH ICS****PULMONIC****AORTIC**

FIG. 2. Phonocardiogram: A systolic murmur is recorded with maximal intensity over the xiphoid and the 4th intercostal space.

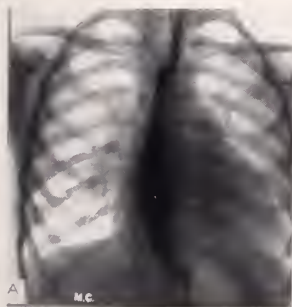


FIG. 3. Interventricular septal defect with dilated pulmonary artery.

A. Posterior-anterior view: There is enlargement of the heart toward the left and prominence of the pulmonary artery segment. There is an indentation of the barium-filled esophagus above the level of the aortic knob which is due to an aberrant crossing of a great vessel.

B. Angiocardiogram: The dotted line indicates the lateral margin of the right ventricle, which is incompletely filled with diodrast. The main pulmonary artery is enlarged.

C. Angiocardiogram: The left side of the heart is visualized. The left ventricle is dilated. The aorta is normal.

and there was some increase in the prominence of the pulmonary vascular markings immediately adjacent to the hila. There was an indentation on the right postero-lateral wall of the barium-filled esophagus just above the aortic knob; this suggested the presence of an anomalous crossing of a large vessel.

The clinical impression at this time was that the location of the maximal murmur and thrill was typical of interventricular septal defect. However the fluoroscopic findings (the prominent pulmonary artery segment, the appearance of right ventricular enlargement, and the increased pulmonary vascular markings) were more consistent with the presence of an interatrial septal defect. Further studies were advised in order to definitely establish the diagnosis.

Cardiac catheterization was performed March 27, 1950. Pressure tracings and blood specimens were obtained from the various sites indicated in Table I. The catheter tip did not enter any septal defect. The systolic pressure in the right ventricle was at the upper limit of normal. The specimens obtained from the right ventricle had a significantly higher oxygen content than the specimens from the right atrium; this indicated that there was a shunt of oxygenated blood into the right ventricle. The findings were consistent with the diagnosis of an isolated interventricular septal defect.

TABLE I  
*Cardiac Catheterization*

SITE	PRESSURE	O <sub>2</sub> CONTENT	PERCENT SATURATION
	<i>mm. Hg</i>	<i>vol. %</i>	
Inferior vena cava	+2	10.4	75.6
Superior vena cava	+2	10.6	77.8
Right atrium	+2	10.3	75.6
Right atrium	+2	10.8	80.0
Right ventricle-tricuspid	35/0	13.2	95.0
Right ventricle	—	12.5	91.5
Right ventricle-outflow tract	30/1	11.9	86.7
Main pulmonary artery	29/10	12.4	89.5
Left pulmonary artery	29/9	—	—
Arterial	—	12.9	93.5
Capacity	—	14.2	—

An angiocardiogram was performed. The right atrium was dilated. The right ventricle was not as densely opacified as would be expected from the appearance of the right atrium, but it was dilated. The outflow tract of the right ventricle was not narrowed. The main pulmonary artery was dilated, but the main branches were normal. The left atrium was normal, but the left ventricle was somewhat dilated. The aorta was normal (fig. 3b, c).

*Comment.* The diagnosis of isolated interventricular septal defect with dilatation of the pulmonary artery was definitely established in this 4½ year old patient, only after catheterization and angiocardiography. The clinical history and the physical findings suggested the diagnosis of isolated interventricular septal defect. The electrocardiogram showed a mild conduction delay in the right ventricle which may be encountered normally, but which may at times be associated with right ventricular enlargement. The latter consideration, in addition to the fluoroscopic evidence pointing toward the diagnosis of right ventricular enlargement with pulmonary artery dilatation, suggested the diagnosis of inter-

atrial septal defect. The quality and location of the murmur made the diagnosis of patent ductus arteriosus or isolated pulmonic stenosis unlikely. Cardiac catheterization established the presence of the interventricular septal defect; angiocardiography outlined the dilated main pulmonary artery and ruled out stenosis of the right ventricular outflow tract. Furthermore, angiocardiography showed the right and left ventricles to be dilated.

The patient was asymptomatic although the precordial bulge betrayed the cardiac enlargement. The pressure in the right ventricle and pulmonary artery were in keeping with the absence of symptoms, although it was recognized that a systolic pressure of 30–35 mm. Hg. was a high normal value for a child of  $4\frac{1}{2}$  years.

#### DISCUSSION

The patient with isolated interventricular septal defect usually does not show pulmonary artery dilatation, or significant cardiac enlargement. The electrocardiogram ordinarily shows no evidence of chamber hypertrophy. However, in a previous publication (5), it was shown that the pulmonary artery was dilated and the right ventricle hypertrophied in some patients with isolated interventricular septal defect. Since the patients who were studied all died in infancy or early childhood, the prognosis was considered poor. However, it was considered possible that the prognosis might be better if survival occurred beyond infancy.

The case presented in this report illustrates the clinical features of interventricular septal defect with dilated pulmonary artery. It is similar to the cases reported in the literature by Dexter (6), Burchell, et al., (7), Cournand (8), and by Healy, et al., (9). Our case differs from the reported cases in that significant pulmonary hypertension is absent.

The outlook in the usual case of interventricular septal defect is good. When, however, there is added to this anomaly a dilated pulmonary artery, the prognosis is guarded. The factors upon which the prognosis depends, are the degree of cardiac enlargement, and the extent of right ventricular, as well as of pulmonary hypertension.

Discussion of the anomalous vessel is postponed for a later presentation.

#### SUMMARY

1. Isolated interventricular septal defect with dilatation of the pulmonary artery is a clinical entity which should be included in the differential diagnosis of congenital cardiac lesions characterized by radiographic prominence of the pulmonary artery.

2. A case is presented which illustrates the features of this congenital anomaly and emphasizes the importance of cardiac catheterization and angiocardiography in establishing the diagnosis.

3. It is suggested that when dilatation of the pulmonary artery coexists with interventricular septal defect, the prognosis is guarded. This is due to the frequently associated presence of pulmonary hypertension and right ventricular enlargement.



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## UNCOMPLICATED PULMONARY STENOSIS<sup>1</sup>

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Several groups of investigators (1-5) have recently studied the problem of uncomplicated pulmonary stenosis\* and, as a result, many features of this disease, previously unclear or controversial, have been clarified. As will be shown, however, there are still points at issue and the diagnosis, even with modern methods of study, may occasionally be difficult to make with certainty.

This abnormality is apparently not rare. Valvular stenosis is more common than isolated infundibular stenosis, but even the latter occurs not infrequently.<sup>2</sup> Greene, et al. (2) found 19 cases in the literature with post-mortem confirmation and added two of their own. We are presenting two cases in this report.

It has been shown that many patients with uncomplicated pulmonary stenosis live without symptoms until their late teens or early twenties, or even later. Characteristically, at this time, dyspnea appears and then within a few years right-sided congestive heart failure progresses until death. Cyanosis is usually absent until the terminal phase and then is peripheral in origin. One of the facts which recent investigations (3, 4) have emphasized is that cyanosis, appearing in the absence of congestive heart failure along with a lowered arterial saturation with oxygen, in the presence of other signs of "isolated" pulmonary stenosis, usually means a physiologically patent foramen ovale with a right to left shunt. There are, however, a few unquestioned cases, shown at postmortem examination to have pulmonary stenosis with closed septa, in which cyanosis, polycythemia, and mild clubbing have been present (2, 4). These are difficult to explain.

The outstanding feature on physical examination is a loud, harsh systolic murmur, with or without a thrill, heard best in the second, third, or fourth left intercostal spaces. Most observers agree that the location of the murmur is of no help in deciding whether the stenosis is valvular or infundibular. Despite some opinions to the contrary, many observers have found that the murmur may be transmitted to the neck. Such transmission, therefore, is of no aid in distinguishing the lesion under discussion from the tetralogy of Fallot or Eisenmenger's complex. The second sound at the pulmonic area may be normal, increased, or decreased in intensity.

On fluoroscopy and in conventional roentgenograms, the cardiac silhouette may be normal; more often there is evidence of right ventricular enlargement,

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<sup>2</sup> The term "uncomplicated pulmonary stenosis" as used in this paper refers to cases in which narrowing of the pulmonary valve or infundibulum is the sole abnormality. The terms "pure", "isolated", or "uncomplicated" pulmonary stenosis have been used at times, whether the foramen ovale has been closed or not, in order to distinguish these cases from those of tetralogy of Fallot, but we think this is not desirable.

which is generally more pronounced than in the tetralogy and may be severe. The right atrium may be enlarged as well and occasionally has been seen to pulsate vigorously. At times the right ventricle may displace the left ventricle so that enlargement of the latter may seem to be present. In the majority of cases, in contrast with the tetralogy, post-stenotic dilatation of the pulmonary artery is found. Dow et al. (5) have noted increased pulsation in such a pulmonary artery despite the stenosis. Our experience confirms this. The aorta is always left-sided. The hilar markings of the lungs may be normal or decreased.

Electrocardiograms may be normal, or, more often, show evidence of right ventricular hypertrophy. Partial right bundle branch block occurs not uncommonly. P-2 and P-3 may be increased in amplitude. Towards the end, the P-R interval may be increased.

Cardiac catheterization provides important information by demonstrating an elevated right ventricular pressure, usually distinct from the systemic arterial pressure, a normal or decreased pulmonary arterial pressure, and the absence of significant degrees of shunt by a normal variation in the oxygen content of the blood in the different chambers. There are several difficulties which arise in connection with these procedures.

The first is that there are cases with a dilated pulmonary artery and a pulmonary systolic murmur which reveal right ventricular pressures within the normal limits, albeit in the upper range, with lower pressures in the pulmonary artery. Greene et al. (2) believe these are instances of idiopathic dilatation of the pulmonary artery, whereas Dow, et al. (5) believe they represent mild degrees of pulmonary stenosis. The final answer to this question will only be provided by post-mortem examination, but perhaps in individual cases angiocardiography may offer assistance. We have studied one unpublished case of this nature in which the angiocardiogram showed no evidence of stenosis.

The second difficulty lies in excluding minor degrees of shunt. At times, observers, including ourselves, have found a variation in the oxygen content of the blood in the various cardiac chambers which is slightly in excess of the normal average values, or a figure for arterial oxygen saturation slightly below normal. It has been difficult to decide whether these represent extreme ranges of normal or whether small shunts are present. The only practical course, until more post-mortem studies decide the question, would seem to be that of Dow, et al. (5) who consider each case primarily from the physiological rather than the strictly anatomical point of view.

In the studies of the aforementioned other group, angiocardiography has been used either sporadically or not at all. Our own experience has been the reverse of this; we have found the procedure to be valuable, particularly in deciding whether a stenosis is valvular or infundibular. Since the introduction of valvulotomy by Brock (6), this is more than an academic question. Some observers (2) apparently can determine the location of pulmonary stenosis by cardiac catheterization, while another group of investigators (5) states, "When there is no separate upper chamber to the right ventricle, it is doubtful if pressure tracings can distinguish a valvular from the fusiform type of infundibular stenosis."

We are presenting two cases of uncomplicated pulmonary stenosis to illustrate some of these points, particularly to stress the importance of the integrated examination.

#### CASE REPORTS

*Case I. History:* M. S., a four year old boy, was admitted to the Mount Sinai Hospital on December 6, 1949, for investigation of a murmur which had been discovered one year previously. There was no history of cyanosis or diminution in cardiac reserve. Abnormal physical findings were limited to the heart. It was not enlarged to percussion. There was a loud, harsh systolic murmur over the precordium, loudest in the second and third inter-spaces to the left of the sternum, transmitted to the neck. There was no clubbing or cyanosis. The hemoglobin level was 11 grams per 100 cc. of blood. The erythrocyte count was 4.4 million per cu. mm.

The electrocardiogram showed a tendency to right axis deviation in the standard leads. The unipolar limb leads indicated a vertical electrical position with a small delayed R in aVR. In the unipolar precordial leads, there was an equiphasic RS with an R of moderate amplitude at the right midclavicular line and across the precordium to V4. There was a deep S in V2 and it diminished in amplitude progressively toward the left. There was an R of moderate amplitude and a small S in V6. The findings were suggestive of right ventricular hypertrophy.

The phonocardiogram disclosed the first sound to be of high amplitude at the mitral and pulmonic areas. A murmur extended through systole and consisted of mixed high and low frequencies; it was recorded at all areas, but was of high amplitude at the pulmonic and aortic areas.

On cardiac catheterization, no abnormal shunts were demonstrated by the exploring catheter. The pressure in the right ventricle was elevated and the pressure in the right and main pulmonary arteries was decreased. A tabulation of the oxygen content and pressure determinations follows:

SITE	OXYGEN CONTENT	SATURATION	PRESSURE
	vols. %	%	mm. Hg
Superior vena cava.....	10.8	68	m.p.* = 0
	11.0	70	
Right atrium (high).....	10.7	68	m.p. = 0
Right atrium (low).....	10.7	68	
Right ventricle (tricuspid).....	9.9	63	50/0
Right ventricle (outflow).....	10.9	69	
Main pulmonary artery.....	10.0	63	m.p. = 5 - 8
Right pulmonary artery.....	11.0	70	m.p. = 5 - 8
Left femoral artery.....	14.3	92	

\* m.p.—mean pressure

Conventional roentgenographic examination of the chest showed no abnormality in the lungs. The pulmonary vascular markings were within normal limits. Except for some rounding of the lower part of the left cardiac border, the cardiac configuration was within normal limits.

Angiocardiogram showed the superior vena cava and right atrium to be normal. The right ventricle was distinctly enlarged so that its left margin constituted about one-third of the lower left cardiac contour. The right ventricular outflow tract was distinctly narrowed and immediately distal to this there was a localized area of post-stenotic dilatation which extended to the pulmonary valve. The latter appeared normal as did the main pul-



monary artery and its right and left branches. Except for the elevation of the left ventricle by the enlarged right ventricle, the left chambers, the aorta, and its branches were normal. There was no evidence to suggest the presence of an intracardiac shunt. The appearance was that of isolated infundibular stenosis.

*Case II. History:* C. R., a girl, aged 14 years was admitted to the Mount Sinai Hospital in January, 1950. The details of her birth and early development were not known, except that a diagnosis of congenital heart disease had been made at the age of six months. For five years she had been dyspneic on exertion and had to rest after climbing one flight of stairs. There was no history of cyanosis or syncope. Two weeks before admission the patient had an episode of nausea and vomiting for one day. At this time a cardiac murmur was discovered and she was sent to the hospital for investigation. Examination showed her to be of low intelligence. She had a somewhat puffy face, her lips were full and thick, the nose wide. The joints were hyperextensible. The hard palate was highly arched. Funnel breast was present. Blood pressure was 110/65. The point of maximal impulse of the heart was in the fourth interspace in the left mid-clavicular line. There was a grade IV harsh, low-pitched systolic murmur in the second and third interspaces to the left of the sternum, accompanied by a systolic thrill. This was transmitted to the left and upward to the left side of the neck. The second aortic sound was greater in intensity than the second pulmonary sound. The liver edge and the splenic tip were barely palpable beneath the costal margins. There were several 8-12 mm. brownish macular lesions on the skin of the left forearm and right infrascapular areas. The hemoglobin content was 12.5 grams per 100 cc. of blood. The basal metabolic rate was plus 8 per cent. Neurological consultant believed that the patient presented a syndrome of congenital mental deficiency, not mongolism. The peripheral venous pressure was 13 cm. of water with a rise to 15.5 cm. on right upper quadrant pressure. The arm-to-tongue circulation time was 15 seconds.

The electrocardiogram showed an unusual axis deviation with the QRS complexes down in all standard leads, with a small R and deep S. aVR showed a high R and small S and aVL and aVF small R and deep S waves. The unipolar precordial leads showed a deep S and a small R all across the chest. The findings were indicative of clockwise rotation of the heart.

Microplethysmography showed no evidence of extra-cardiac shunt.

X-ray examination of the wrists showed normal development of the carpal bones.

X-ray examination of the chest was normal except for a slight convexity along the left upper border of the heart. On fluoroscopy, the pulmonary artery was seen to pulsate vigorously.

Cardiac catheterization elicited no evidence of shunt. It revealed a highly elevated right ventricular pressure. The pulmonary artery was not entered. The oxygen contents and pressures in the various locations were as follows:

SITE	OXYGEN CONTENT	SATURATION	PRESSURE
	vols. %	%	mm. Hg
Inferior vena cava . . . . .	11.5	73	0
Superior vena cava . . . . .	11.2	71	0
Mid right auricle . . . . .	10.0	63	0
High right auricle . . . . .	10.3	66	2
Right ventricle . . . . .	10.9	69	70/7
Peripheral artery . . . . .	14.5	91	—

Angiocardiogram showed the superior vena cava to be widened, and the right atrium and ventricle to be enlarged. The outflow tract of the right ventricle was narrowed. The pulmonary valve and the main pulmonary artery were normal. The right and left branches of the pulmonary artery were slightly dilated. The left atrium and left ventricle were normal.

Oximetry studies on exercise failed to provide evidence of right to left shunt. At rest the instrument was set at 93%. After exercise, the arterial saturation fell to 91.5% and after the patient breathed 100% oxygen, it rose to 95.5%.

*Comment.* In each of the two cases presented, the absence of cyanosis, the characteristic murmur, the right ventricular enlargement, the narrowing of the infundibulum demonstrated by angiocardiography, the elevated right ventricular pressure, and in one case, the decreased pulmonary artery pressure, demonstrated the presence of infundibular pulmonary stenosis. Because infundibular stenosis is frequently accompanied by other lesions, especially the other defects comprising the tetralogy of Fallot, and because of the slightly lowered arterial saturation in each case, it became necessary to consider whether complicating lesions were present. Angiocardiography gave no evidence of shunts. The right ventricular pressure was well below the level of the systemic pressure. Exercise in one case produced an insignificant lowering of the arterial oxygen saturation. The single low oxygen content in the right ventricle in Case I, and the high oxygen contents in the superior and inferior vena cava in Case II are difficult to explain in terms of other known defects. In common with Dow, et al. (5) when confronted with similar cases, we are forced to conclude that our oxygen figures probably represent extremes of normal variation, or if they do represent shunts, these are physiologically insignificant.

Of importance is the aid which angiocardiography gave in ascertaining the site of the stenosis.

#### SUMMARY

Recent studies of uncomplicated pulmonary stenosis are briefly summarized. Two instances of uncomplicated infundibular pulmonary stenosis are presented.

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## TRICUSPID ATRESIA WITH TRANSPOSITION OF THE GREAT VESSELS: SUCCESSFULLY TREATED BY SURGERY\*

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The recent great interest in congenital cardiac malformations and their alleviation by surgery has resulted in great advances in our methods of diagnosis of individual congenital defects. As a result, the more complicated lesions are being diagnosed with a fair degree of accuracy. Amongst these are cases of tricuspid atresia (1). This lesion, associated with loss of function of the right ventricle, now presents a recognizable clinical picture.

Tricuspid atresia is never an isolated anomaly, but always occurs in association with other congenital cardiac malformations. In some instances improvement can be anticipated following surgical intervention, whereas in other combinations no such improvement should be expected. The purpose of this paper is to present the history of a child in whom surgical intervention resulted in marked clinical improvement and to discuss the steps in arriving at a pre-operative diagnosis as well as the essential information supplied by angiocardiography.

### CASE REPORT

*History.* R. R., a 5 year old boy was admitted to the Mount Sinai Hospital on March 1, 1949, because of fever of 3 days duration and also for study of a congenital cardiac anomaly. The pregnancy and delivery had been normal, the birth weight was 9 pounds. At 2 months of age the patient suddenly had a convulsion, following which he became cyanotic. Cyanosis was severe and persisted to the time of admission. He had marked limitation of exercise and dyspnea on exertion. He had never been able to run and he could walk only 25 yards.

*Examination.* The patient was an underdeveloped, undernourished boy in no distress, but markedly cyanotic. Especially involved were the ears, the lips, the tip of the nose, the fingers and toes. He weighed 30 pounds, 2 ounces. Temperature was 103°F., pulse was 118 per minute, respirations 28 per minute. The upper respiratory tract failed to reveal any focus of infection. The lungs were clear to percussion and auscultation. The heart was enlarged slightly to the left on percussion. No precordial bulge was noted. The point of maximal intensity was in the 4th left interspace inside the midclavicular line. It was forceful and diffusely felt over most of the precordium. A thrill was palpable in the 3rd interspace just to the left of the sternal border. A loud rasping systolic murmur was heard over the entire precordium, maximal in the 3rd left interspace and transmitted to the neck vessels. Blood pressure was 94 systolic and 58 diastolic. Femoral pulses were palpable. The liver edge was palpable 4 cm. below the costal margin and did not pulsate. No other abdominal viscera were palpable.

The hemoglobin ranged between 18.5 and 21.1 Gm. per cent with 6.8 million red blood cells. There were 13,500 white blood cells per cu. mm. with 22% polymorphonuclear leukocytes, 30% non-segmented cells and 48% lymphocytes. The hematocrit was 70%. The urine was normal. Naso-pharyngeal culture revealed staphylococcus aureus A.

*Course.* A history of fever for 3 days before admission, the elevated white blood count, an apparent focus of infection in the paronychia of the left index finger, and the existence of a congenital cardiac defect made one suspect the possibility of bacterial endarteritis.

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Several blood cultures were sterile. The patient was given procaine penicillin (300,000 units q.d.), and the temperature became normal within 72 hours. With the subsidence of the infection, cardiac diagnostic study was started.

Electrocardiogram revealed left axis deviation in the standard leads.  $P_1$  and  $P_2$  were tall and peaked, indicating atrial enlargement. There was a high R wave in AVL and a small



FIG. 1. The absence of the normal right lower cardiac convexity and the prominence of the left contour are illustrated. The pulmonary hilar vascular markings are diminished in prominence.



FIG. 2. In the left anterior oblique projection the straightening of the right lower cardiac contour is well seen.

R and deep S in AVF. Phonocardiography revealed a high amplitude, medium frequency systolic murmur at the aortic area, and also at the pulmonic area. Fluoroscopy revealed a globular heart with a straightened right border. Microplethysmography failed to reveal any evidence of extracardiac arteriovenous anastomosis. Fluorescein circulation time was 4 seconds compared to the normal of 8-15 seconds.

The presence of left axis deviation in a child with cyanotic congenital heart disease



immediately suggested the diagnosis of tricuspid atresia. The fluoroscopic findings were consistent with this diagnosis. Inasmuch as the patient had survived to the age of 5 years, it was necessary to postulate the presence of additional anomalies which would alter the cardiac physiology sufficiently to be compatible with life. The presence of an inter-atrial septal defect of good size was assumed in view of the absence of a pulsating liver. In addition it was postulated that an interventricular septal defect existed, the right ventricle acting as a tube for the passage of blood from the left ventricle to the pulmonary artery. There was no evidence in favor of the existence of a patent ductus or a truncus arteriosus.



FIG. 3. One-half second after the initial appearance of diodrast in the heart, the left atrium is opacified through an interatrial septal defect.

Conventional roentgenography of the chest revealed (fig. 1) a striking absence of the expected lower right cardiac convexity. The prominence of the left lower contour was apparent. The ascending aorta and aortic knob were normal. Less apparent was the deficiency in the left pulmonary artery segment.

Figure 2 illustrating the appearance in the left anterior oblique position, does not show the convexity usually produced by the right ventricle.

On March 16, angiocardiology was performed. Figures 3, 4 and 5 were selected from the exposures made in the postero-anterior projection. Figure 3 represents the exposure made about one-half second after the initial appearance of diodrast-containing blood in the right atrium and reveals 1) the right atrium apparently normal in size and position, 2) reflux

into the inferior vena cava and hepatic veins, 3) immediate entry of diodrast-containing blood into a normal-sized left atrium by way of a large inter-atrial septal defect. In Figure 4 the large left ventricle and the aortic arch are opacified. A small amount of diodrast has appeared in the pulmonary artery. In Figure 5 maximal pulmonary opacification has occurred. This is distinctly diminished as compared with the normal. The great vessels arise normally from the aortic arch and are well visualized, suggesting a greater flow of diodrast-containing blood in them than in the pulmonary tree. This suggests diminished circulation in the pulmonary tree as compared with the systemic circuit.



FIG. 4. The enlarged left ventricle and the normal aorta and great vessels are shown. Opacification of the pulmonary circuit is scant.

Figure 6, selected from the series made with the patient in the left anterior oblique position, illustrates the status immediately after visualization of the left ventricle as seen in Figure 4. The aorta arises anteriorly from a diminutive chamber which fills after the left ventricle. This is believed to represent an atretic right ventricle acting as a conduit between the left ventricle and the aorta in the presence of an interventricular septal defect. The pulmonary artery arises posteriorly to the aorta and was distinctly narrower than normal.

On the basis of these examinations, it was postulated that blood entered the right atrium, traversed a large inter-atrial septal defect to enter the left atrium and in turn the left ventricle. From this chamber the small pulmonary artery was filled as was the diminutive

right ventricle, the latter through an interventricular septal defect. The aorta apparently arose entirely from the small right ventricle.

These findings confirmed the clinical impression of tricuspid atresia, a large inter-atrial septal defect, inter-ventricular septal defect and diminutive right ventricle. In addition they established the presence of transposition of the great vessels and suggested the presence of pulmonic stenosis.



FIG. 5. Maximum opacification of the pulmonary artery circuit is seen at this time. The pulmonary arterial vessels are very small.

In view of the above findings, the advisability of creating a shunt between a subclavian artery and the corresponding pulmonary artery was considered. As is well known, an increase in pulmonary blood flow can be effected only if an adequate pressure gradient exists between the systemic and pulmonary circulations. The only evidence that this pressure gradient existed was the suggestive evidence noted on angiocardiography. Inasmuch as this patient's exercise tolerance was markedly limited, it was decided to proceed with operation.

On April 6, 1949, an anastomosis of the left subclavian artery to the left pulmonary artery was performed by Dr. Arthur S. W. Touroff. The pulmonary artery was hypoplastic with low tension to palpation. As soon as the clamps were released, the pulmonary artery distal to the site of anastomosis filled out and the patient's color improved markedly.

Post-operatively the patient did very well. A left hemothorax was aspirated twice, with beneficial results. On the 17th post-operative day, the patient was out of bed in a wheel chair. The success of the operation was attested to by 1) decrease in polycythemia (hemoglobin from 21 Gm. to 14.5 Gm. and red blood cells from 6.8 million to 4.5 million), 2) the appearance of a diastolic murmur in the pulmonary area confirmed by phonocardiography, 3) microplethysmographic evidence of an extracardiac arteriovenous shunt and 4) definite increase in exercise tolerance. The patient could run at least 25 yards. The patient was discharged on May 12, 1949, the 36th post-operative day.



FIG. 6. In the left anterior oblique projection the diminutive right ventricle is seen anteriorly. The aorta apparently arises directly and completely from this chamber which acts as a conduit between the left ventricle and the aorta.

The patient was studied again on January 13, 1950. He had gained 2 pounds in weight. The hematocrit was 40%. A to-and-fro machinery-like murmur was heard in the pulmonic area and at the inferior angle of the left scapula posteriorly. The left arm was cool and no radial pulse was palpable. Exercise tolerance had improved markedly so that the boy could run and play for considerable periods. The cyanosis had diminished to a very considerable extent.

*Comment.* The cardiac defect under discussion is one ideally suited to the clinical analytic methods so fully described by Taussig (1). The finding of left axis deviation in a cyanotic infant or child with a congenital cardiac malformation must be presumed to be due to a non-functioning right ventricle until proven



otherwise. Cases of tetralogy of Fallot with left axis deviation have been described (3) but these are certainly less common than the anomaly being discussed.

The roentgen configuration of the heart usually reflects the absence of right ventricular volume as deficiencies in the lower right cardiac contour in the postero-anterior view and in the retrosternal space in the right anterior oblique projections. The pulmonary artery is usually small and this is manifested by decrease in the diameter of the waist of the heart. In our case the conventional roentgenograms (figs. 1 and 2) reveal the typical configurations.

A non-functioning right ventricle is caused by tricuspid atresia or stenosis of such severity that blood is incapable of passing from the right atrium to the right ventricle. It follows that an inter-atrial septal defect must be present to allow blood to flow from right atrium to left atrium and thence to left ventricle and aorta. Under these circumstances, a pulmonary artery arising from the diminutive right ventricle will be markedly hypoplastic and pulmonary blood flow will be severely restricted and incapable of sustaining life except for the very shortest period. Sufficient pulmonary flow for sustenance of life can be maintained during that period of infancy in which the ductus is normally patent. Any child with this lesion who survives beyond two years of age must have an anomaly which allow for sufficient pulmonary blood flow consistent with maintenance of life though not necessarily consistent with adequate function. This pulmonary blood flow may be through a large patent ductus arteriosus, a truncus arteriosus with adequate bronchial arteries, a patent pulmonary artery arising normally but receiving blood from the left ventricle through an interventricular septal defect, or transposition of the pulmonary artery so that it arises from the left ventricle and the aorta overrides both ventricles or is completely transposed.

The absence of adequate egress of venous blood by way of the right ventricle and the inevitable inter-atrial septal defect produce an admixture of venous and arterial blood in the systemic circulation, with resultant cyanosis. The anomalous source of the pulmonary circulation usually is associated with more or less diminution in pulmonary blood flow and it is the latter feature which renders some cases suitable for those surgical shunting procedures which result in increased oxygenation of blood by increasing the flow of blood through the lungs.

Whether or not this procedure can be expected to improve the patient's conditions depend upon two factors: 1) the size of the inter-atrial septal defect and 2) hypoplasia of the pulmonary artery. In that anomaly in which the inter-atrial septal defect is small, an insufficient quantity of blood returned to the right atrium will pass through the defect to the left atrium. This should be suspected if the liver pulsates and may be demonstrated by angiocardiology. Under these circumstances, an attempt should be made to increase the size of the defect in the inter-atrial septum as described by Blalock (4). In those instances in which the pulmonary artery pressure is high and pulmonary blood flow is adequate, the anastomosis created by a Blalock-Taussig operation will not be expected to function.

We feel that the basic features of this malformation can be diagnosed clinically. Angiocardiology may be of assistance in the evaluation of these patients for

surgical intervention, first, by confirming the diagnosis, second, by delineating the course of the circulation, third, by demonstrating the size of the pulmonary artery, fourth, by furnishing indirect evidence of the adequacy of pulmonary flow, fifth, by indicating the freedom of communication between the atria, and finally, by demonstrating the positions and sizes of the vessels arising from the aortic arch thereby enabling the surgeon to plan the surgical approach and to pre-select the components for anastomosis.

The pre- and post-operative management of patients suffering with tricuspid atresia, as with any other congenital cardiac anomaly associated with severe degrees of cyanosis, includes the judicious use of oxygen, digitalis when indicated and the maintenance of adequate fluid intake. We feel that the importance of this latter factor is too often overlooked. In view of the polycythemia and severe hemoconcentration, even mild degrees of dehydration may result in cerebral thrombosis. Fluids should never be withheld from these patients for more than 12 hours in preparation for any procedure, diagnostic or therapeutic. The intravenous route should be used when any doubt exists regarding the ability to administer adequate quantities by mouth. The importance of this factor in the daily care of patients with cyanotic congenital cardiac malformations should never be overlooked.

#### SUMMARY

The history of a child with tricuspid atresia and transposition of the great vessels who showed marked improvement following surgical intervention is presented. The steps in arriving at a diagnosis are discussed and the value of angiocardiograms is demonstrated. The necessity of administering adequate quantities of fluids to prevent dehydration is emphasized.

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## ABERRANT INSERTION OF PULMONIC VEINS\*

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Anomalous drainage of one or more pulmonic veins into the right atrium, the vena cava, or one of the tributaries of the latter associated, almost invariably, with interatrial septal defect is compatible with a normal life span without undue morbidity. Angiocardiography has successfully demonstrated these lesions during life (1), (2). Cardiac catheterization is also valuable in establishing and confirming this diagnosis (3), (4), (5), (6), (7), (8), (9). Two variants of this condition have been observed in adults: (a) insertion of the right lower lobe pulmonic vein into the inferior vena cava, and (b) insertion of the left upper lobe pulmonic vein into the left innominate vein. The clinical findings are those of interatrial septal defect. The radiographic appearance in these cases is characteristic and diagnostic.

Two cases are presented to illustrate the salient clinical and laboratory features in this anomaly.

### CASE REPORTS

*Case 1. Interatrial septal defect, with aberrant insertion of the right lower lobe pulmonic vein into the inferior vena cava.*

*History.* A. R., a man, aged 30 years, was known to have had a cardiac murmur since infancy. For this reason, despite the absence of signs of diminished cardiac reserve, physical activity had been restricted.

The patient was of small stature but appeared well developed. Cyanosis and clubbing were not observed. A slight precordial bulge was observed to the left of the sternum. A coarse systolic murmur of moderate intensity and a faint decrescendo diastolic murmur were heard just below the pulmonic valve area. Inconstant distant systolic and diastolic humming murmurs were present to the right of the lower sternum. The blood pressure was 125/80 mm. of mercury. The electrocardiogram indicated the presence of right ventricular hypertrophy with an RR' complex over V1 and to the right of this location.

Radiographic and fluoroscopic examinations of the heart and lungs revealed considerable enlargement of the heart to the right and moderate enlargement to the left in the postero-anterior projection. The pulmonary artery and its main branches were prominent. A curvilinear density was present in the right lower lung field parallel to the cardiac border in this region (fig. 1). Its appearance suggested that it was a vascular structure. It did not pulsate, and during the Valsalva and Mueller maneuvers, changes in its size or density were equivocal.

Angiocardiography was performed with the patient in the postero-anterior and left anterior oblique positions. The postero-anterior examination demonstrated the presence of considerable right atrial and right ventricular enlargement, as well as dilatation of the pulmonary artery and its main branches. The right paracardiac structure seen in the conventional films was opacified after the pulmonary arteries had been visualized and simultaneously with the demonstration of the left atrium (fig. 2). In the series of films made with the patient in the oblique position, enlargement of the right atrium, right ventricle, and pulmonary arteries was again seen. During this phase of the examination, the inferior vena

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cava was visualized by virtue of reflux from the right atrium (fig. 3), a frequent occurrence in angiocardiology of no known clinical significance. A subsequent film showed decrease in the density of the above structures. This was followed by visualization of the pulmonic

TABLE I

*Case I. A. R.: Interatrial septal defect, aberrant insertion of the right lower lobe pulmonic vein into the inferior vena cava*

	OXYGEN CONTENT	PER CENT SATURATION
1. Femoral artery.....	17.4	92.5
Capacity.....	19.2	
2. Superior vena cava.....	11.1	65
3. Mid-right atrium.....		
a. Lateral.....	12.6	73
b. Medial.....	14.3	84
4. Inferior vena cava.....		
a. Low.....	13.4	78
b. Mid.....	13.4	78
5. Right ventricle.....	14.5	85
6. Pulmonary artery.....	14.2	84



FIG. 1. Case I. The band-like right paracardiac density represents the anomalous pulmonary vein. The heart is moderately enlarged, and the right and left pulmonary arteries are prominent.

veins and of the left atrium. In the latter film the previously described anomalous vessel was well seen. It coursed towards, and emptied into the inferior vena cava which became re-opacified by virtue of this anomalous drainage. This was confirmed by cardiac cathe-



terization which showed that blood obtained at the diaphragmatic level of the inferior vena cava contained a higher quantity of oxygen than did samples withdrawn from the superior vena cava, right atrium, right ventricle, and main pulmonary artery. Because the catheter did not traverse an interatrial septal defect, the presence of this associated condition was not demonstrated.

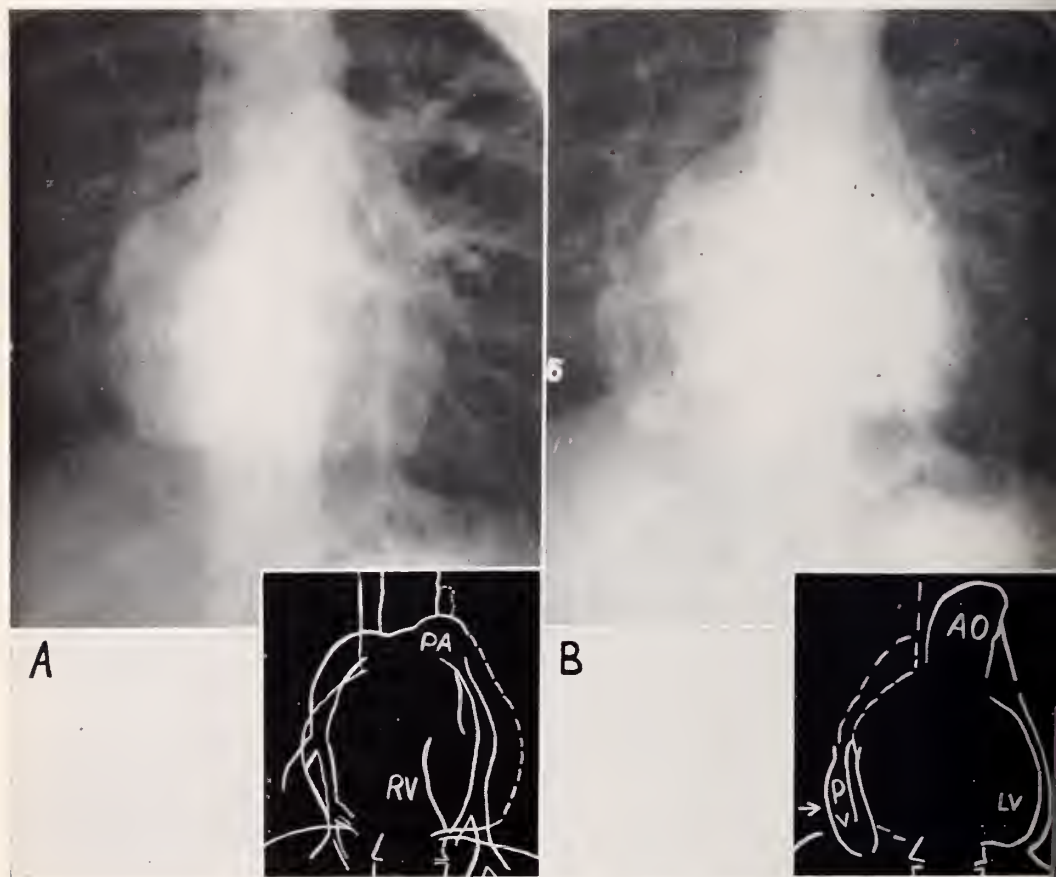


FIG. 2. Case 1. (A) Angiocardiogram (postero-anterior projection) showed no opacification of the right paracardiac density during visualization of the right side of the heart and pulmonary arteries.

(B) The aberrant pulmonary vein became opacified simultaneously with other pulmonary veins.

*Case 2. Interatrial septal defect with aberrant insertion of a left upper lobe pulmonic vein into the left innominate vein.*

*History.* A. M., a man aged 25 years, was found to have a cardiac murmur in the course of an examination following his application for enlistment in the Armed Services. He had been asymptomatic with respect to the cardiovascular system.

The patient was of slim habitus and somewhat underdeveloped. Digital cyanosis and clubbing were absent. The heart was enlarged to the left, and there was a diffuse increase in the force of the apical impact. A systolic thrill and a diastolic shock were felt over the pulmonic valve area. A coarse loud systolic murmur and a markedly accentuated second sound were heard over this area. Very faint systolic and diastolic murmurs were present on

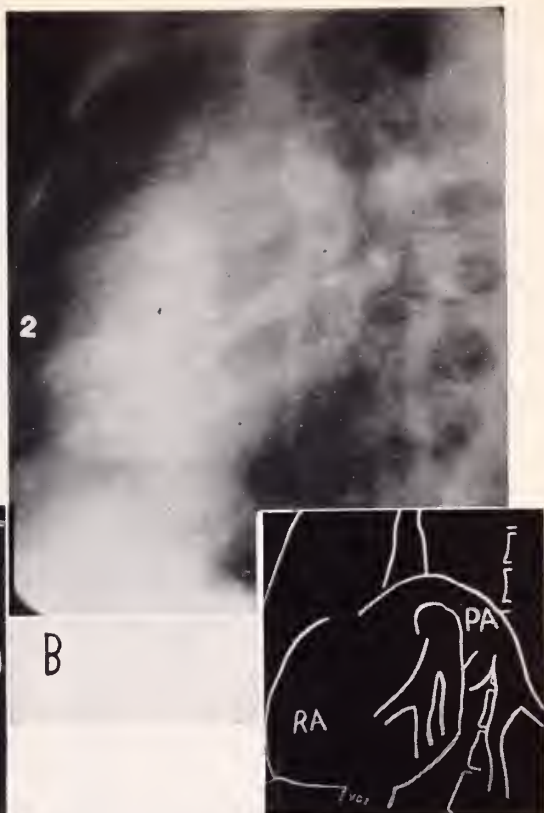
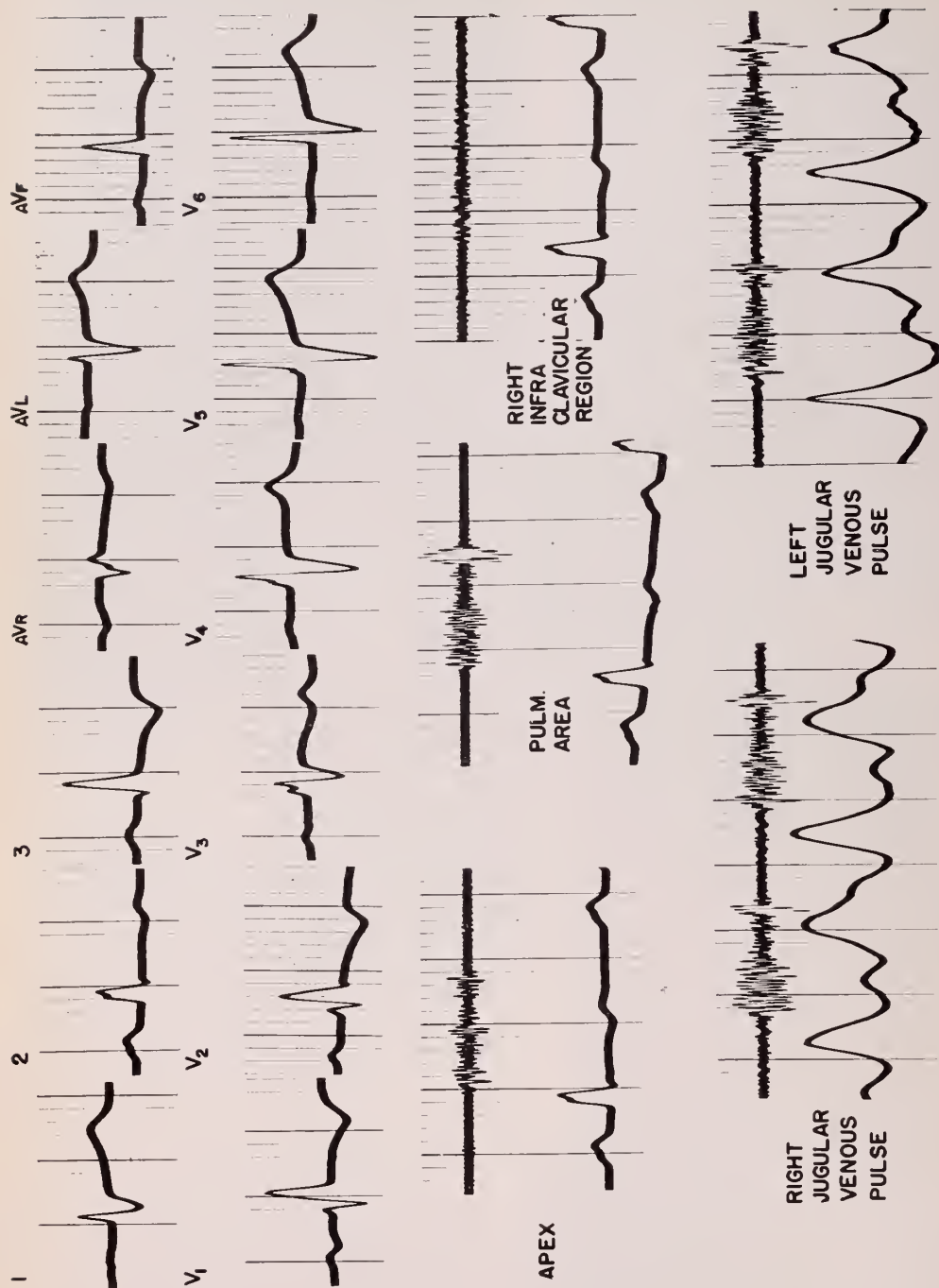


FIG. 3. Case 1. (A) Angiocardiogram (left anterior oblique projection) showed dilatation of the right atrium, right ventricle and pulmonary arteries. There is reflux into the inferior vena cava. The anomalous vessel is not seen.

(B) Decrease in the density of the above structures is demonstrated.

(C) With visualization of the pulmonary veins and left atrium, the anomalous pulmonary vein is again demonstrated as it courses toward and opacifies the inferior vena cava.



A.M.

FIG. 4. Case 2. Electrocardiogram reveals RSR, right axis deviation, and an RR configuration of the QRS complexes, and inverted Twaves over V1 and V2. These changes indicate right ventricular hypertrophy. Phonocardiogram recorded over the pulmonary area demonstrates a systolic murmur of high amplitude followed by a second sound of increased amplitude and duration. Systolic and diastolic murmurs of low amplitude were recorded over the intracavitary region. Venous pulse tracings from the A.M. showed a late systolic wave of high amplitude. A late systolic wave similar to those encountered in Tricuspid regurgitation.



FIG. 5. Case 2. (A) The left ventricular apex is elevated and rounded. The superior paramediastinal densities are noted.

(B) Posterior displacement of the esophagus is present at the level of the main pulmonary arteries.



FIG. 6. Case 2. (A) Angiocardiogram (postero-anterior projection). Opaque medium is present in innominate vein. The mottled appearance in this and other films suggests dilution near the origin of this vein. The right paramediastinal density is faintly opacified, but the left paramediastinal density is not opacified.

(B) Coincident with opacification of the pulmonary veins, the left paramediastinal density is opacified. The latter enters the left innominate vein at the site at which dilution was observed to occur.



each side of the upper end of the sternum. The electrocardiogram (fig. 4) revealed regular sinus rhythm, right axis deviation, and RR' configuration of the QRS complexes over V1 and V2.

Radiographic and fluoroscopic examinations (fig. 5A) demonstrated considerable enlargement of the heart to the left and elevation of the left ventricular apex. The superior mediastinum was symmetrically widened by sharply demarcated, laterally convex, homogeneous, and pulsatile structures. The aortic knob appeared small, but the pulmonary artery segment was prominent as were the pulmonary vessels in the vicinity of each hilus. The retrosternal space was encroached upon by enlargement of the right ventricle. At the level of the right pulmonary artery the esophagus was displaced posteriorly, presumably as a result of the increased size of this vessel (fig. 5B).

Angiocardiograms were made by injection of the opaque medium into a right antecubital vein and then into a left antecubital vein. The first series demonstrated marked dilatation of the superior vena cava. In fact, the density previously seen in the superior mediastinum was partially explained when its right side was identified as dilated superior vena cava. Thereafter, despite an adequate injection with regard to speed of injection, opacification was poor, and this suggested that the superior caval blood was considerably diluted before

TABLE II

*Case II. A. M.: Interatrial septal defect, aberrant insertion of left upper lobe pulmonic vein into the left innominate vein*

	OXYGEN CONTENT	PER CENT SATURATION
1. Femoral artery . . . . .	18.8	97.5
Capacity . . . . .	19.6	
2. Left subclavian vein . . . . .	10	52
3. Left innominate vein . . . . .	18.8	97.5
4. Superior vena cava . . . . .	18.3	94
5. Right atrium . . . . .		
a. High . . . . .	17.5	92
b. Low . . . . .	18.3	94

its entry into the right atrium. The second series of films, obtained by injection into a left antecubital vein, delineated a moderately dilated innominate vein. As this vessel entered the mediastinum, the density of the contrast substance decreased rather abruptly, and this again indicated dilution at this site. The right atrium, right ventricle, pulmonary artery and its branches were seen to be considerably dilated (fig. 6A). After the pulmonary circuit had been traversed, the left superior paramediastinal structure became opacified, simultaneously with pulmonary veins. This unusually wide pulmonary vein joined the innominate vein at the site where dilution had been observed earlier in the sequence (fig. 6B).

Cardiac catheterization confirmed the clinical diagnosis (Table II).

#### DISCUSSION AND SUMMARY

Aberrant insertion of pulmonary veins into the right side of the heart or its tributaries is an entity in which three important variants exist. These are:

- 1) Aberrant insertion of all pulmonary veins usually into the coronary sinus,
- 2) Aberrant insertion of a right lower lobe pulmonary vein into the inferior vena cava, and
- 3) Aberrant insertion of a left upper lobe pulmonary vein into the left innominate vein.

Other variants undoubtedly occur (10).

Of the three variants discussed, the first is apparently not compatible with life beyond infancy. The other two variants (six cases in our series) have not been associated with diminished cardiac reserve.

Functionally this condition is similar to interatrial septal defect which appears to be the least incapacitating congenital cardiac anomaly.

The radiographic appearance is characteristic and is determined by the origin, course, and termination of the anomalous vessel.

Angiocardiography and cardiac catheterization are of value in the confirmation of the clinical diagnosis.

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## ABSTRACTS

### AUTHORS' ABSTRACTS OF PAPERS PUBLISHED ELSEWHERE BY MEMBERS OF THE MOUNT SINAI HOSPITAL STAFF

Members of the hospital staff and the out patient department of the Mount Sinai Hospital are invited to submit for publication in this column brief abstracts of their articles appearing in other journals.

*A Note on Freud's Scientific Imagination.* L. A. SPIEGEL. Internat. J. Psycho-Analysis, 29: 124, July, 1948.

Convinced by numerous analyses that dreams, like hysterical symptoms, were meaningful and amenable to scientific interpretation, and persuaded by general concepts of evolution that they represented a primitive form of mental activity, Freud developed an hypothesis that enabled him to pass from the content of the dream and the rules for its interpretation to the form and function of the total "machinery" of the mind. Approximately a half century later, the distinguished neurophysiologist Adrian, proposed a theory of brain functioning which is substantially identical with Freud's hypothesis of the functioning of the psychic apparatus, as published in 1900. There are three major points of agreement between the two hypotheses; the tendency of the organism to get rid of excitation through motor activity; the motor activity continuing till the inner disturbance is gotten rid of; the organism guided in this motor activity by its search for appropriate incoming sensory stimuli. When the external sensory stimuli correspond in some way to the internal excitation, the motor activity ceases and an equilibrium is reached. In one case, this correspondence is described as an identity of the new perception with the memory trace of a previous perception. In the other, the correspondence is described in patterns of brain waves. . . . "When the afferent pattern is the sensory counterpart of the behavior which was implicit in the disturbing pattern . . . the two patterns will then cancel out." This coincidence of psychological and physiological hypotheses is but an example of the indivisibility of truth which can be gotten at by various searchers, each through his own scientific discipline.

*The Pathology of Gargoylism. Report of a Case and Review of the Literature.* L. STRAUSS. Am. J. Path., 24: 855, July, 1948.

A case of gargoylism in a 3 year old girl is described and the anatomical findings compared with those reported in the literature. Emphasis is placed on hitherto not described alterations in mesenchymal tissues, characterized by the presence of vacuolated cells, often associated with proliferation of collagenous fibers and sometimes with an increase of ground substance. The inclusion of gargoylism in the group of storage diseases is suggested because of evidence of storage in many cells of the body, and because of the similarity of changes in the central nervous system with those in amaurotic idioey. It appears that there is a widespread disturbance of intracellular metabolism the chemical nature of which is still unknown.

*Treatment of Exophthalmic Goiter in Childhood; A Report of a Follow-up Study in Twelve Cases.* A. TOPPER. Am. J. Dis. Child., 76: 26, July, 1948.

A follow-up study was made of 12 children treated for Graves Disease. The children have been observed for from 3 to 25 years. Four were treated surgically; 8 were treated medically. The former all have periods of hypothyroidism which respond readily to therapy

The latter have needed no therapy since puberty was established, and have had no recurrence of symptoms since. At the time of puberty, the needs for somatic growth are subordinated to the needs for maturation. To this end, the thyroid gland assumes a lesser role than the gonads. Anything therefore that will control symptoms of hyperthyroidism until puberty and brings about a spontaneous cure, should be tried. Whether it be propylthiouracil, radio-active iodine, or other drug still to be discovered, it is important to avoid thyroidectomy before puberty, because of the significance of the thyroid gland for future growth and development.

*Plastic Repair for Postoperative Anal Incontinence.* R. TURELL, J. B. GORDON AND K. DAVIS. K. Am. J. Surg., 76: 89, July, 1948.

The causes of and pertinent plastic procedures for the repair of anal incontinence are discussed. In this paper the authors present a surgical plan for the restoration of the continuity of the external anal sphincter muscle. In this plastic operative procedure the Bunnell type of tendon suture is utilized in the repair of the severed anal sphincter muscle for the successful restoration of continence. This stitch is used because it apparently avoids strangulation of the muscle fibers involved in the sutures. The technic is well illustrated.

*Three-way Infusion Valve for Biologic Fluids.* W. BIERMAN. Am. J. Surg., August, 1948.

This new valve is specially designed for the transfer of biologic material from one channel to another. It is a three-way metal valve which has the advantage that it can be quickly taken apart for cleaning and reassembled with equal speed. Metal pins on the side of the valve allow for the automatic setting in the desired channel. A cross piece attached to the under surface permits the valve to remain in place when employed for intravenous work in an extremity.

*Modern Treatment of Peptic Ulcer with Intra-gastric Drip Therapy.* A. CORNELL AND A. WINKELSTEIN. Am. Pract., 2: 779, August, 1948.

Regardless of the ultimate cause (probably psychosomatic), the immediate agent or mechanism of peptic ulcer formation seems to be the "acid-pepsin" factor. Most peptic ulcers (especially duodenal ulcer) reveal a marked increase in gastric acidity and secretion. This increase is most marked during the interdigestive period, particularly during the night. In view of the lack of exact knowledge as to the etiology of peptic ulcer, the ideal medical therapy should consist in the establishment of a continuous harmless achlorhydria throughout the 24 hours of the day. Thus, the ideal therapy in peptic ulcer, both medical and surgical, should be the establishment of a harmless achlorhydria. Sixteen years of experience with intra-gastric drip therapy has proven its value as a logical method of controlling this harmful interdigestive night acid secretion. To date, no other form of medical therapy has succeeded in this aim. It is of special value in the group of uncomplicated, but nevertheless refractory cases of peptic ulcer. It is also of great value in treating complicated cases, which for various reasons should not be treated surgically.

*Palindromic Rheumatism.* S. DAVISON. New York State J. Med., 48: 1836, August, 1948.

Palindromic rheumatism, described by Hench and Rosenberg in 1941, consists of multiple afebrile attacks in an adult, of acute arthritis of generally one small or large joint, with rapid onset and development, lasting a few hours to a few days, recurring at varied intervals, without constitutional reaction, normal sedimentation rate, complete restitution of function, and after years, no pathological changes in or about the joints. There is no relief with salicylates or other specifics. Although not a common rheumatic disorder, it should be considered in puzzling cases since much time and money will otherwise be spent on useless therapy. A case is presented with all the features of the disease, which had been misdiagnosed for 11 years.



*Arthritis, Conjunctivitis, and Urethritis (so called Reiter's Syndrome) in a Four Year Old Boy.* A. L. FLORMAN AND H. M. GOLDSTEIN. *J. Pediatrics*, 33: 172, August, 1948.

The case history is presented of a 4 year old boy who, following a short period of diarrhea, developed arthritis, conjunctivitis, and urethritis. Recovery from this syndrome, which was originally described by Reiter, was accompanied by a gradual decline in Shigella Flexner agglutinins from a level of 1:1280 to 1:40. The significance of this observation is not clear. Attempts to recover a pathogenic microorganism, pleuropneumonia-like organism, or a virus from the joint fluids, urethral discharge, and conjunctival smears were unsuccessful. It is believed that this is the first recorded instance of this disease in a child.

*A New Adhesive Tape Remover of Particular Value in Patch Testing.* A. W. GLICK, G. WEISBERG AND S. M. PECK. *J. Invest. Dermat.*, 10: 6, June, 1948.

In patch testing it is important that the adhesive tape plaster has good sticking qualities. Unfortunately however, the better the tackiness of the adhesive, the more marked is the traumatic reaction of removal. We would like to report our experiences with an adhesive tape remover which we believe has obviated this reaction to a great extent. Propylene glycol ethyl ether was used as the adhesive tape remover. It has the advantage of being non-inflammable and non-toxic. The use of propylene glycol ethyl ether is a practical aid in carrying out patch tests. It renders the removal of adhesives relatively painless and, most important, it reduces the traumatic reaction of removal to a very large extent.

*Deep Keratitis Associated With Atypical Lichen Planus. Report of a Case.* J. GOLDSMITH. *Arch. Opth.*, 40: 138, August, 1948.

A rare case of deep keratitis occurring in atypical lichen planus associated with alopecia areata, poliosis, vitiligo and hyperpigmentation was described. Vascularization of the cornea was not observed in this keratitic lesion which finally underwent complete regression. Penicillin and sulfadiazine were ineffectual. The relationship of this keratitis to keratitis profunda, keratitis disciformis and parenchymatous keratitis of the syphilitic and tuberculous types was discussed. It was reasoned that quinacrine ("atabrine"), in the role of a sensitizing agent to the corneal tissues, was probably responsible for the development of the keratitis, together with toxic products of the destructive cutaneous lesions.

*Group Therapy with Soldiers and Veterans.* W. C. HULSE. *Mil. Surgeon*, 103: 2, August, 1948.

Experiences with group psychotherapy in Army and Veterans Hospitals in the United States and the European Theatre of Operations and with a group of veterans in a private practice setting show that while a didactic and repressive approach with large numbers of patients participating, seems to be helpful as a method of orientation and as an emergency measure, employment of small groups is a more effective procedure. Especially is this true where the therapist can apply psychoanalytic insight to deepen the therapeutic advantages provided by the group structure in a permissive setting conducive to full expression of affect. Apart from its use in the treatment of well-selected neurotic patients, the group method provides a new approach to the treatment of the psychotic patient wherein he can experience much needed freedom and equality in a permissive group setting. The hospital staff also profits greatly from its experience in the group—disciplinary problems are easily avoided, if patients are selected, not according to theoretical homogeneity but according to mutual compatibility.

*The Role of High Blood Penicillin Levels Achieved with Caronamide in Penetrating the Blood-Brain Barrier.* H. D. JANOWITZ, S. SCHNEIERSON, M. L. SUSSMAN AND F. H. KING. *J. Lab. & Clin. Med.*, 33: 933, August, 1948.

Significant penicillin levels in the cerebrospinal fluid of normal subjects were achieved by the method of frequent rapid intravenous injection of large doses of crystalline penicillin in conjunction with the oral administration of Caronamide (4-carboxyphenyl-

methanesulfonanilide) which inhibits the tubular excretion of the antibiotic. Following the intravenous injection of one million units of penicillin every hour for ten hours in eight patients receiving four grains of Caronamide every three hours, blood penicillin levels of from 100 to 300 oxford units, and spinal fluid penicillin levels of from 1.0 to 6.0 oxford units were recorded after the tenth injection. Therapeutically significant levels were still present 14 hours after the last injection. The clinical implication of these findings for the treatment of meningeal infections is discussed.

*The Morphological Backgrounds of "Genuine Lipoid Nephrosis".* E. MOSCHOWITZ. *Am. J. M. Sc.*, 216: 146, August, 1948.

The term "nephrosis" has been so modified by subsequent students of the malady from its original connotation, that when it is employed one should demand a definition. The fundamental clinical phenomena of "lipoid nephrosis" are reviewed and their genesis outlined. The primary factor is a prolonged hypoproteinemia. The hypoproteinemia is the result of a persistent proteinuria consequent to an increased permeability of the glomerular capillary walls, which is not always explainable histologically with our current technical methods. The hypoproteinemia, and especially, hypoalbuminemia, is responsible for the edema and anasarca and for the low protein content of the exudate. In addition, the hypoproteinemia is probably indirectly responsible for the low basal metabolic rate by creating an edema which acts as a suit of clothes preventing the dissipation of heat. This explanation is based on our demonstration that integumentary thickenings of whatever nature are usually accompanied by a low basal metabolic rate. The lipemia represents in all probability a compensatory phenomenon. Evidence has been submitted to show that anatomical "lipoid nephrosis" (nearly always) represents one of the biological progressions of a glomerulonephritis, in which the conventional productive changes have either disappeared or have not developed. In other instances, it may be the result of extrarenal factors in which a hypoproteinemia ensues. Clinical and anatomical "lipoid nephrosis" are by no means synonymous. In the last analysis, "nephrosis" is not a disease in the sense that it has a consistent background in either morbid anatomy or etiology. Instead of employing a generic term to cover a multitude of unrelated morphological backgrounds, accuracy of thought would be promoted by ascribing the best available descriptive term for each renal disorder.

*Dialysis of Protein Solutions for Electrophoresis.* M. REINER AND R. L. FENICHEL. *Science*, 108: 164, August, 1948.

A mechanical dialyzer was devised which allows the equilibration, within two hours, of protein solutions against a buffer solution, using cellophane tubing and a simple mechanical stirrer. This process, measured by pH and specific conductance, ordinarily takes 24 hours or longer.

*The Mechanism of Irregular Sinus Rhythm in Auriculoventricular Heart Block.* I. R. ROTN AND B. KISCH. *Am. Heart J.*, 36: 257, August, 1948.

In auriculoventricular heart block, the rhythm of the auricles is often irregular. Illustrative electrocardiograms are presented to demonstrate patterns of this irregularity as they appear in partial and complete A-V heart block. The literature dealing with the mechanism of the auricular irregularity has been reviewed. Measurements of large numbers of consecutive auricular intervals and their component segments in electrocardiograms of A-V heart block reveal that postsystolic slowing of the auricles is a characteristic feature of the arrhythmia and that the degree of slowing is essentially a function of the point of incidence of the initial ventricular deflection. In the light of the knowledge that the tone of the vagus nerves depends, to a significant degree, upon the pressure within the aorta and carotid arteries, these observations have led the authors to regard the mechanism of auricular irregularity in A-V heart block as a reflex inhibition of the cardiac pacemaker initiated by a pressure rise within the aorta and carotid arteries, incident to the systolic

injection of these vessels. Observations on the auricular arrhythmia under the influence of atropine and observations on the relative inhibitory effects of normal and premature ventricular systoles in the same subject support this view. Seeming inconsistencies in auricular response to ventricular systole in A-V heart block are discussed in the light of the properties of a reflex vagus mechanism.

*"Silent Dacryocystitis."* F. H. THEODORE. Arch. Opthth., 40: 157, August, 1948.

A mild type of dacryocystitis, usually mucoid in character, is often the unsuspected cause of persistent conjunctivitis or of unexplained tearing. This "silent" type of dacryocystitis is overlooked if investigation of the tear passages is limited only to a determination of patency. If, however, the lacrimal washings are collected and examined both clinically and bacteriologically, the finding of mucus, mucopus or frank pus containing pathogenic bacteria will indicate the presence of "silent" dacryocystitis. In cases of this type obstruction does not play an obvious role. Once the diagnosis is established and treatment of the dacryocystitis instituted, the conjunctivitis, which in almost every case of the present series had existed for months, subsided in a matter of weeks, recovery paralleling the clearing of the lacrimal washings. Experience suggests that this low grade type of mucous dacryocystitis is not uncommon and, if not recognized, may eventually lead to more obvious inflammatory changes in the lacrimal passages.

*Grave Angina de Petto per Nove Anni, con minime Alterazioni Elettrocardiografiche. Esito dovuto a Insufficienza coronarica senza Infart (secondaria a Pancreatite acuta emorragica).* M. VOLTERRA. Riv. Clin. Med. 48: 162, August, 1948.

This is a clinical presentation of a case. A brief discussion is given on a differentiation of coronary insufficiency from coronary occlusion, and the Master "two step" test for the demonstration of coronary insufficiency is briefly described. The similarity of the elettrocardiografic changes after the "two step" test and during a spontaneous anginal attack was clearly shown in this case. A few considerations on the management of coronary insufficiency, when it is precipitated by disease of other organs (gall-bladder, pancreas, etc.) closes this presentation.

*Sul Trattamento Moderno dell 'Ipertiroidismo.* M. VOLTERRA. Riv. Clin. Med. 48: 255, August, 1948.

It is a critical review of the management of hyperthyroidism from the year 1923, the year of introduction of Iodine, to 1948, five years after the discovery of thiouracil and related compounds. Comparative activity and toxicity of the latter drugs are discussed and the preference for the use of propyl- and methyl-thiouracil indicated. The indications and first clinical experiences with the use of radioactive Iodine in the treatment of hyperthyroidism are reported.

*Serial Electrocardiographic Changes in Young Adults with Acute Rheumatic Fever.* N. S. BLACKMAN AND C. I. HAMILTON. Ann. Int. Med., 29: 416, September, 1948.

Serial electrocardiographic findings in 62 cases of the initial attack of acute rheumatic fever in soldiers between the ages of 17 and 21 are presented. On a routine of repeated electrocardiograms every other day for the first week of illness and twice a week thereafter, 61 cases (98.4%) were found to have electrocardiographic changes suggestive of carditis; 61.2% of the patients showed RS-T segment and T-wave changes, while 41.9% showed prolongation of the P-R interval. Fluctuations in the tracings during the course of the disease were considered to be abnormal, as the normal serial electrocardiogram shows extreme constancy in form. The changes are discussed in detail. The authors advocate the routine suggested above in the taking of serial electrocardiograms to assist in the diagnosis of acute rheumatic cardiac involvement.

*A Comparative Study of Subtotal Gastrectomy with and without Vagotomy.* R. COLP, P. KLINGENSTEIN, L. J. DRUCKERMAN, AND V. A. WEINSTEIN. *Ann. Surg.*, 128: 470, September, 1948.

In an attempt to improve long term results in the treatment of duodenal ulcer, the authors have added vagotomy to subtotal gastrectomy. The purpose of this study was to present the advantages and disadvantages of this combined procedure.

In order to accomplish this, the morbidity, mortality, and early follow-up records in 46 duodenal ulcer patients treated by vagotomy plus subtotal gastrectomy is compared to similar records in 54 patients treated by subtotal gastrectomy alone. There were no untoward reactions at the time of operation attributable to division of the vagi. In one case the esophagus was lacerated. There were no deaths in either series. The post-operative morbidity was slightly more severe in the vagotomy group in that there was a higher incidence of pulmonary complications. The post-operative acidity studies revealed a significantly higher incidence of achlorhydria in the combined (vagotomy) group. There was one recurrence (jejunal ulcer) in the group treated by gastrectomy alone.

The authors feel that this study should be continued as a long term one to determine whether subtotal gastrectomy combined with infradiaphragmatic vagotomy will lower the incidence of jejunal ulcer.

*Sulfadiazine and Penicillin Prophylaxis in Cesarean Section.* R. GORDON DOUGLAS AND ROBERT LANDESMAN. *Am. J. Obst. & Gynec.*, 56: 422, September, 1948.

A study was completed at the New York Hospital concerning the use of prophylactic penicillin and sulfadiazine in cesarean section. These agents were begun after 24 hours of labor without ruptured membranes, after 12 hours with ruptured membranes, or when a prolonged labor or difficult delivery was anticipated. A considerable reduction in the severity of intrauterine, urinary, wound, and peritoneal infections resulted. With this early prophylactic therapy, a longer trial of labor was continued prior to operation without danger. A review of sections indicated a reduction, within recent years, in morbidity in spite of a longer period of labor prior to operation. The low flap operation was performed in most cases after prolonged labor.

*Anesthesia in Thoracic Surgery; with Special Reference to Surgery of the Esophagus.* S. S. LYONS. *New York State J. Med.*, 48: 17, September, 1948.

Surgery for diseases of the esophagus has attained universal recognition. The anesthetization of such cases requires vigilant supervision and a thorough knowledge of the physiology of respiration and circulation. The pharmacologic action of the anesthetic agents used and other drugs employed, together with the reflex mechanisms which may be encountered during such procedures, are of fundamental importance. "Open chest" operations which heretofore were fraught with disaster, are no longer considered a problem to the trained anesthetist. For surgery of the esophagus the anesthetic sequence of choice is induction with one of the gaseous agents, e.g., nitrous oxide, ethylene or cyclopropane (provided the latter is not contraindicated), and complemented with ether. An endotracheal airway must always be introduced and the carbon dioxide absorption technique employed. Postoperative respiratory complications have always been troublesome. Pneumothorax, trapped air and pneumonias were relatively common with the older so called "air-tight" closures of the chest. The importance of complete and continuous inflation of the lungs, and their maintenance in that expanded state until the last skin suture is inserted, dressing applied and under-water drainage established, had not been fully appreciated. This latter technique does provide an "air-tight" closure of the chest, and has completely eliminated respiratory complications.

*The Effect of Anemia and Polycythemia on Digital Intravascular Blood Viscosity.* M. MENDLOWITZ. *J. Clin. Investigation*, 27: 549, September, 1948.



The calorimetric method for measuring digital blood flow was used to study changes in intravascular blood viscosity with varying erythrocyte concentration in patients with anemia and polycythemia. In each observation the blood vessels were dilated maximally by indirect heating. Change in the ratio of pressure to flow with increasing erythrocyte concentration was used as a measure of change in viscosity, the factor of vascular caliber having been maintained relatively constant. Pressures were corrected for "yield value" which varied with erythrocyte concentration. Flow values were corrected for the specific heat of the blood which also varied with erythrocyte concentration. The final observations confirmed similar studies in animals, indicating that intravascular blood viscosity differs from *in vitro* measurements. The gradient of decrease in viscosity with decreasing erythrocyte concentration in anemia was moderate. The blood viscosity in polycythemia increased gradually with moderate increase in erythrocyte concentration and more steeply at higher levels. The blood viscosity was found to be 80 per cent of normal at a hematocrit level of 17 and 169 per cent of normal at a hematocrit level of 73, these being the extremes of anemia and polycythemia observed.

*Treatment of Acute and Subacute Localized Osteomyelitis with Chemotherapy.* M. J. ORINGER. Oral Surg., Oral Med., & Oral Path., 1: 842, September, 1948.

Osteomyelitis, dreaded persistent bone disease, appears to respond favorably to chemotherapy. Two cases, maxillary and mandibular, for which routine postoperative treatment proved unavailing, are reported. Penicillin cones inserted into one involved tooth socket appeared to act as foreign bodies and aggravate the condition. Local chemotherapy produced slight improvement. Combined local and systemic chemotherapy, maintaining adequate blood levels long enough to effect complete bacteriostasis, effectively controlled the disease. Suppuration persisted until after removal of the sequestra. Thereafter, healing progressed rapidly. Chemotherapy alone does not effect complete cures. The principles of sterilization, evacuation, and obliteration must still be observed. Chemotherapy provides sterilization, but surgical evacuation of pus and bone sequestra must be performed before obliteration of bone cavities and soft tissue regeneration takes place.

*The Renal Clearance of Endogenous "Creatinine" in Man.* J. BROD AND J. H. SIROTA. J. Clin. Investigation. 27: 645, September, 1948.

The endogenous "creatinine" chromogen/inulin renal clearance ratio was determined in 14 subjects without renal disease. The average ratio, representing 94 clearance periods, was  $1.00 \pm 0.018$  with a range of 0.88 to 1.10. Simultaneous endogenous "creatinine"/thiosulfate renal clearance ratios, representing a total of 47 periods, averaged  $0.95 \pm 0.018$  with a range of 0.84 to 1.01. In 13 subjects with renal disease, having a glomerular filtration range from 2.64 to 96.9 cc per minute, the endogenous "creatinine"/inulin clearance ratios, representing 57 clearance periods, averaged  $1.04 \pm 0.109$  with a range of 0.89 to 1.25. Simultaneous endogenous "creatinine"/thiosulfate renal clearance ratios in these latter subjects, representing a total of 51 clearance periods, averaged  $1.10 \pm 0.292$  with a range of 0.77 to 1.63. The results indicate that the endogenous "creatinine" chromogen clearance may be used as an index of glomerular filtration in normal adults and as a useful clinical approximation of this function in subjects with renal disease.

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## CONTENTS

	PAGE
DR. ALBERT A. BERG. A MEMOIR. <i>Ernest E. Arnheim, M.D.</i> .....	351
SCIENTIFIC RESEARCH IN MODERN HOSPITAL PRACTICE. <i>George Baehr, M.D.</i> .....	353
SOME OF THE PRINCIPLES AND METHODS CONTRIBUTED BY THE SERVICE OF DR. A. A. BERG. <i>Leon Ginzburg, M.D.</i> .....	356
TOWERING MEN OF MEDICINE. <i>Bertram M. Bernheim, M.D.</i> .....	369
DR. A. A. BERG: AN APPRECIATION. <i>Leopold Stieglitz, M.D.</i> .....	370
CONSENT FOR OPERATION. <i>Joseph Turner, M.D.</i> .....	373
SURGICAL TREATMENT IN ACUTE HEMORRHAGE OF PEPTIC ULCERS. <i>H. Finsterer, M.D.</i> .....	377
THE ROMANCE OF THE MODERN ERA OF BLOOD TRANSFUSION. <i>Richard Lewisohn, M.D.</i> .....	393
VAGOTOMY IN THE TREATMENT OF PEPTIC ULCER NEAR THE CARDIA AND OF PEPTIC ULCER OF JEJUNUM (MARGINAL ULCER, STOMAL-ULCER). <i>Felix Mandl, M.D.</i> .....	409
VAGOTOMY AND SUBTOTAL GASTRIC RESECTION WITH VAGOTOMY IN CASES OF GASTROJEJUNAL AND GASTROJEJUNOCOLIC ULCERS AND FISTULAS AFTER MULTIPLE PREVIOUS SURGICAL PROCEDURES. <i>Waltman Walters, M.D., and James R. Hoon, M.D.</i> .....	423
OBSERVATIONS ON GASTRECTOMY FOR CHRONIC DUODENAL ULCER WITH PARTICULAR REFERENCE TO GASTRECTOMY WITH AND WITHOUT INFRADIAPHRAGMATIC VAGOTOMY. <i>Percy Klingenstein, M.D., Ralph Colp, M.D., Leonard J. Druckerman, M.D., and Vernon A. Weinstein, M.D.</i> .....	429

PRESERVATION OF THE PYLORIC ANTRUM IN RESECTION OF HIGH GASTRIC LESIONS. <i>Rudolph Nissen, M.D.</i> .....	442
PUDENDAL HERNIA. REPORT OF A CASE OPERATED UPON BY THE ABDOMINAL ROUTE. <i>John H. Garlock, M.D., and Alvin A. Bakst, M.D.</i> .....	450
THE RESULTS OF SPHINCTEROTOMY IN PANCREATITIS. <i>Henry Doubilet, M.D., and John M. Mulholland, M.D.</i> .....	458
AVULSION OF THE DIAPHRAGM. <i>Moses Behrend, M.D., Albert Behrend, M.D., and Gladys Rosenstein, M.D.</i> .....	463
CARCINOMA OF THE GALL BLADDER. A REPORT OF 32 CASES. <i>Max Danzís, M.D.</i> .....	467
EPIDERMOID CARCINOMA OF THE ANAL CANAL. <i>H. E. Bacon, M.D., R. Venturo, M.D., and I. Sauer, M.D.</i> .....	478
THE PRESENT STATUS OF THE SURGICAL TREATMENT OF CANCER OF THE COLON AND RECTUM. <i>Samuel H. Klein, M.D.</i> .....	486
DIRECT ARTERIOVENOUS ANASTOMOSIS. <i>W. Wayne Babcock, M.D.</i> ...	499
METHOD FOR THE TERMINO-VEINUS AND VENO-ARTERIOUS ANASTOMOSES. <i>R. Paolucci, M.D., and E. Tosatti, M.D.</i> .....	506
PERIPHERAL ARTERIAL EMBOLISM. <i>Samuel Silbert, M.D.</i> .....	517
RETROPERITONEAL SARCOMA (ADRENAL TUMOR?) WITH ACTIVE HEMORRHIAGE. A SURGICAL EMERGENCY RESECTION. TWENTY-SEVEN YEAR FOLLOW-UP. <i>Harold Neuhoof, M.D.</i> .....	520
PRIMARY IDIOPATHIC SEGMENTAL HEMORRHAGIC INFARCTION OF THE GREATER OMENTUM. <i>Gabriel P. Seley, M.D.</i> .....	523
RETRO-CECAL ABSCESS, A LATE SEQUELA OF ACUTE GANGRENOUS APPENDICITIS. <i>Thomas J. Sullivan, M.D.</i> .....	526
SURGERY OF THE NEWBORN. <i>Ernest E. Arnheim, M.D.</i> .....	528
CONGENITAL ATRESIA OF THE BILE DUCTS. <i>Alfred A. Strauss, M.D.</i> ...	552
ACUTE APPENDICITIS WITH MALROTATION OF THE CAECUM. CASE REPORT. <i>Gertrude Felshin, M.D.</i> .....	563
TECHNICAL PRINCIPLES IN MYOMECTOMY WITH SPECIAL REFERENCE TO HEMOSTASIS. <i>I. C. Rubin, M.D.</i> .....	565
PROLAPSE OF THE UTERUS. A REVIEW OF 722 CASES TREATED BY THE PARAMETRIAL FIXATION OPERATION. <i>Morris A. Goldberger, M.D., and David Zakín, M.D.</i> .....	571
FIBRO-ADENOMA OF THE OVARY WITH ASCITES AND HYDROTHORAX (MEIGS' SYNDROME). <i>Abraham E. Jaffin, M.D.</i> ...	596
TORSION OF THE FALLOPIAN TUBE PRODUCING GANGRENE OF THE SMALL INTESTINE. <i>Louis Burke, M.D., Arthur N. Davids, M.D., and Gabriel Seley, M.D.</i> .....	605
CESARIAN SECTION AFTER COLECTOMY FOR ULCERATIVE COLITIS. <i>Emanuel Klempner, M.D.</i> .....	610
ENDOMETRIOSIS IN A LAPAROTOMY SCAR. REPORT OF A CASE WITH UTERO-ABDOMINAL FISTULA. <i>Nathan Mintz, M.D., and Joseph A. Gains, M.D.</i> .....	613
RECURRENT CERVICAL METASTATIC CANCER. TWO CASE REPORTS. <i>Harry C. Saltzstein, M.D.</i> .....	618
INTESTINAL OBSTRUCTION COMPLICATED BY PREGNANCY. <i>Robert I. Walter, M.D.</i> ...	625
CALCULOSIS OF THE URINARY TRACT IN EGYPT. <i>J. Bitschai, M.D.</i> ...	630
RENAL PTOSIS. <i>Elmer Hess, M.D., Russell B. Roth, M.D., and Anthony F. Kaminsky, M.D.</i> .....	644

SUPRAPUBIC PROSTATECTOMY WITH HEMOSTASIS BY TRANSURETHRAL FULGURATION AND PRIMARY CLOSURE OF THE BLADDER. <i>Abraham Hyman, M.D., H. E. Leiter, M.D., and Stanley I. Glickman, M.D.</i> .....	652
LIPOMYOSARCOMA OF THE KIDNEY: REPORT OF TWO CASES. <i>Leo Edelman, M.D.</i> .....	659
PAPILLARY CARCINOMA OF THE URETER AND BLADDER THIRTEEN YEARS POST-NEPHRECTOMY FOR PAPILLARY CARCINOMA OF THE KIDNEY. <i>Gordon D. Oppenheimer, M.D., and Harold Lear, M.D.</i> ...	671
CONGENITAL ECTOPIC HYDRONEPHROTIC KIDNEY SIMULATING AN INTRAPERITONEAL LESION. <i>M. Swick, M.D.</i> .....	675
PULMONARY DECORTICATION IN CIVILIAN PRACTICE. <i>Arthur S. W. Touroff, M.D., and Gabriel Seley, M.D.</i> .....	680
PNEUMONECTOMY FOR PRIMARY LOCALIZED LYMPHOMA. <i>Arthur H. Aufses, M.D.</i> .....	693
EXTRAPLEURAL PULMONARY RESECTION (PLEUROPNEUMONECTOMY). <i>Irring Arthur Sarot, M.D.</i> .....	700
THE MIDDLE LOBE SYNDROME. <i>Isidor Kross, M.D., and Milton B. Rosenblatt, M.D.</i> .....	711
NOTES ON SUBPHRENIC ABSCESS. <i>Coleman B. Rabin, M.D.</i> .....	717
BILATERAL TRIGEMINAL NEURALGIA. <i>Roland M. Klemme, M.D.</i> .....	729
TUMORS OF THE INTRACRANIAL PORTION OF THE OPTIC NERVE. <i>Ira Cohen, M.D.</i> .....	738
SPONTANEOUS OCCLUSION OF THE INTERNAL CAROTID ARTERY IN THE NECK. <i>Sidney W. Gross, M.D.</i> .....	746
AN IMPROVED OSTEOPLASTIC EXPOSURE OF THE TEMPORO-OCCIPITAL REGION. <i>Benno Schlesinger, M.D.</i> .....	750
DEPRESSED FRACTURE OF THE TIBIAL PLATEAU. A SIMPLE SURGICAL METHOD FOR ELEVATION AND FIXATION OF THE DEPRESSED FRAGMENT. <i>Robert K. Lippmann, M.D.</i> .....	761
LIPOMA PETRIFICUM OSSIFICANS OR LIPOMA WITH HETEROTOPIC OSSIFICATION. <i>Albert J. Schein, M.D.</i> .....	769
HYPERPARATHYROIDISM. <i>I. Snapper, M.D., and D. Rosenthal, M.D.</i> .....	774
BLOOD IODINE AND I-131 EXCRETION IN DIAGNOSTIC PROBLEMS OF HYPERTHYROIDISM. <i>Solomon Silver, M.D., Stephen B. Yohalem, M.D., and Mack H. Fieber, M.D.</i> .....	781
THE SIMULTANEOUS OCCURRENCE OF ACTIVE PEPTIC ULCER AND ACTIVE HYPERTHYROIDISM. <i>A. L. Garbat, M.D.</i> .....	787
CHANGING PATTERNS IN THE DEFINITION OF ACUTE LUPUS ERYTHEMATOSUS. <i>Paul Klemperer, M.D.</i> .....	793
SARCOIDOSIS IN RELATION TO TUBERCULOSIS. <i>Eli Moschcowitz, M.D.</i> .....	799
PEPTIC ULCER—PRESENT DAY MEDICAL THERAPIES. <i>Asher Winkelstein, M.D.</i> .....	808
MULTIPLE EROSIONS AND ACUTE PERFORATIONS OF THE ESOPHAGUS, STOMACH, AND DUODENUM IN RELATION TO DISORDERS OF THE NERVOUS SYSTEM. <i>Joseph H. Globus, M.D., and Bruce L. Ralston, M.D.</i> .....	817
GASTROENTEROLOGY AS A SURGICAL SPECIALTY AT THE MOUNT SINAI HOSPITAL. <i>Burrill B. Crohn, M.D.</i> .....	843
SURGICAL ASPECTS OF PEPTIC ULCER. <i>Sidney Grossman, M.D.</i> .....	848



CHANGES IN GASTRIC ACIDITY AND MOTILITY IN A CASE OF BILATERAL SUBPHRENIC VAGOTOMY ALONE FOR DUODENAL ULCER (11 YEAR FOLLOW-UP OF IMMEDIATE AND LATE RESULTS). <i>Albert Cornell, M.D.</i> .....	855
THE GASTRIC POUCH FROM ITS ORIGINS TO THE PRESENT (AN HISTORICAL STUDY IN THE METHODOLOGY OF GASTRIC PHYSIOLOGICAL RESEARCH. WITH PARTICULAR REFERENCE TO THE CONTRIBUTIONS OF PAVLOV). <i>Franklin Hollander, Ph.D.</i> .....	872
MALROTATION OF THE INTESTINE. <i>Leo H. Pollock, M.D.</i> .....	886
MELANOMA OF THE SMALL INTESTINE AND STOMACH. <i>Alexander Richman, M.D., and Joan J. Lipsay, M.D.</i> .....	907
MUCOSAL AEROGRAPHIC STUDIES OF THE STOMACH AND SMALL BOWEL. <i>Arthur J. Benlick, M.D.</i> .....	917
THE RELATION OF NEUROCIRCULATORY ASTHENIA TO ANXIETY NEUROSIS. <i>B. S. Oppenheimer, M.D., and Menard M. Gertler, M.D.</i> .....	924
THE PSYCHOSOMATIC APPROACH TO NEUROCIRCULATORY ASTHENIA—A SUPPLEMENT TO "THE RELATION OF NEUROCIRCULATORY ASTHENIA TO ANXIETY NEUROSIS." <i>Sidney G. Margolin, M.D.</i> ..	930
THE CARDIAC PATIENT AND OPERATION. <i>Arthur M. Master, M.D., and Harry L. Jaffe, M.D.</i> .....	934
PSYCHODYNAMIC FACTORS IN SURGERY. <i>Solon S. Bernstein, M.D., and S. Mouchly Small, M.D.</i> .....	938
FETAL DEFECTS RESULTING FROM VIRAL DISEASE OF THE PREGNANT MOTHER. <i>Murray H. Bass, M.D.</i> .....	959
OBSERVATIONS ON BLOOD PRESSURE IN CHILDREN FOLLOWING AN ACUTE GLOMERULO-NEPHRITIS. <i>Sam de Lange, M.D., and Jerome L. Kohn, M.D.</i> .....	971
OBSERVATIONS ON THE USE OF DIGITALIS IN THE TREATMENT OF CHRONIC CONSTIPATION AND ALLIED CONDITIONS. <i>Albert A. Epstein, M.D.</i> ..	980
THE RICE DIET IN THE TREATMENT OF THE AMBULATORY HYPERTENSIVE PATIENT. <i>David Adlersberg, M.D., Leon Bader, M.D., and Harold B. Trachtenberg, M.D.</i> .....	990
A SIMPLE TEST FOR EXTENT OF SYMPATHECTOMY. <i>Henry D. Janowitz, M.D., and M. I. Grossman, M.D.</i> .....	1004
THE ROLE OF ACCESSORY SPLEENS IN POST-SPLENECTOMY RECURRENT PURPURA HEMORRHAGICA. <i>N. Rosenthal, M.D., P. Vogel, M.D., S. Lee, M.D., and Joan J. Lipsay, M.D.</i> .....	1008
A SURVEY OF SOME RECENTLY PROPOSED CHEMICAL TESTS FOR MALIGNANCY. <i>Harry Sobotka, Ph.D.</i> .....	1021
THE USE OF RADIOACTIVE AND STABLE ISOTOPES IN HEMATOLOGY. <i>L. R. Wasserman, M.D., I. A. Rashoff, M.D., and T. F. Yoh, M.D.</i> .....	1037
X-RAY DIFFRACTION ANALYSIS OF MIXTURES CONTAINING SODIUM SALTS OF FATTY ACIDS. <i>Gerda Gershein Mayer, Ph.D., Herman S. Kaufman, Ph.D., and S. M. Peek, M.D.</i> .....	1048
ABDUCENS NERVE PALSY FOLLOWING SPINAL ANESTHESIA. <i>Milton H. Adelman, M.D., and Sidney S. Lyons, M.D.</i> .....	1055
BALISTOCARDIOGRAPHY—A REVIEW. <i>Louis B. Turner, M.D.</i> .....	1060
THE CLINICAL PICTURE OF CEREBRAL ARTERIOSCLEROSIS WITH PARTICULAR REFERENCE TO THE AGED. <i>Frederick D. Zeman, M.D.</i> .....	1075
THE TREATMENT OF NEUROBLASTOMA. <i>Sidney M. Silverstone, M.D., and William Harris, M.D.</i> .....	1083

THE TREATMENT OF PTERYGIUM BY SIMPLE EXCISION. <i>David Wexler, M.D.</i> .....	1092
CLOSURE OF PHARYNGOSTOME BY DISTANT OPEN LINED FLAP. <i>Joseph L. Goldman, M.D., and Samuel M. Bloom, M.D.</i> .....	1096
SURGERY FOR DEAFNESS IN CONGENITAL ATRESIA OF THE EXTERNAL AUDITORY CANAL (WITH REPORT OF A CASE). <i>Samuel Rosen, M.D.</i>	1104
WHAT IS JUSTIFIABLE SURGICALLY IN MÉNIÈRE'S DISEASE? <i>Harry Rosenwasser, M.D.</i> .....	1109
RECONSTRUCTION OF THE LARYNX AND THE TRACHEA. REPORT OF A CASE OF EXTENSIVE CICATRICIAL STENOSIS. <i>Max L. Som, M.D.</i>	1117
ABSTRACTS . . . . .	1127
INDEX . . . . .	1133

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THIS VOLUME IS DEDICATED TO

THE MEMORY OF

## DR. ALBERT A. BERG

BY HIS FRIENDS, ASSOCIATES, AND PUPILS

### IN RECOGNITION OF

THE UNEXCELLED SERVICE RENDERED BY HIM  
TO SURGERY AND TO THE MOUNT SINAI HOSPITAL  
FOR AN UNINTERRUPTED PERIOD OF 56 YEARS



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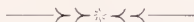
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DR. ALBERT A. BERG

## DR. ALBERT A. BERG

## A MEMOIR

Dr. Albert A. Berg was born in New York City, on August 10, 1872. He was educated at the New York Public Schools, and received his A.B. degree at the College of the City of New York in 1891, and his M.D. degree at the College of Physicians and Surgeons, Columbia University, in 1894. His training as an interne was at The Mount Sinai Hospital from 1894 to 1896. He was appointed to the attending staff of the Hospital as Adjunct Surgeon in 1899, promoted to Associate Surgeon in 1911, and Attending Surgeon in 1914. He retired from active service in 1934 with the title of Consulting Surgeon. At the time of his death, on July 1, 1950, he was also Consulting Surgeon at the Montefiore Hospital, New York City; the Beth Moses Hospital, Brooklyn; The Monmouth Memorial Hospital, Long Branch, N. J.; and the Barnert Memorial Hospital, Paterson, N. J. He was President of the International College of Surgeons from 1943 to 1947, Fellow of the New York Academy of Medicine, and Honorary Fellow of the Roman and Turin Surgical Societies, Italy.

Dr. Berg's professional career was intimately associated with The Mount Sinai Hospital. His enormous surgical practice allowed him little time for other activities, but he nevertheless managed to become one of the country's leading collectors of rare books and manuscripts. This was unknown to the public until his later gifts of large collections of these works to the New York Public Library. His older brother, Dr. Henry Berg, exerted a powerful influence on his development, and the two were inseparable companions.

Many stories have been told of Dr. Berg's surgical skill. The first characteristic of his surgery which comes to mind was orderliness of procedure. Each operation was made up of a series of steps which followed one another in an orderly sequence, only varying under unusual circumstances. This orderliness of procedure made his surgery a treat for the observer, and simplified the work of the assistant. Operations proceeded step by step, each stage being carried out in a deliberate manner before the next stage was begun. The repetition of steps because they had not been completed in the first instance was eliminated, thus reducing the time of operation, although the individual movements were not rapid. Dr. Berg excelled in the performance of secondary operation in the abdomen in which innumerable adhesions would baffle the average surgeon. His last operation, three weeks before his death, performed under great physical suffering, was such an operation carried out with all the skill of his younger days. He felt that the scalpel and not the scissors was devised for sharp dissection, and the scalpel was thus his instrument of choice. The boldness of his surgery was based upon a long experience fortified by a full knowledge of anatomy. Full visualization through liberal incisions for exposure was routinely practiced.

Dr. Berg's enemies were death and cancer. He excised malignant tumors which according to other standards were inoperable; many of these patients were cured



and many were uncured, but he attacked malignant tumors with all the power at his command. He was a man of limitless energy, and he demanded the same of others. His patients were grateful for his tireless, faithful care. His work was done modestly without conceit or self praise.

Dr. Berg was reluctant to try new procedures if those he practiced were of proven efficacy. However, he did not hesitate to change to other methods when the old procedures were proven to be ineffectual. He deserves great credit for adopting the procedure of partial gastrectomy for gastric and duodenal ulcer in 1920. He was severely criticized by many American surgeons as being too radical in the surgery of this condition. For years these surgeons continued to practice the operation of gastroenterostomy, and now we find that the operation of partial gastrectomy is the accepted surgical procedure for gastric and duodenal ulcer, and the operative technique which he proposed in 1923 is now widely practiced. Dr. Berg's decision to employ partial gastrectomy was based upon sound experimental and physiologic study performed under his direction by Dr. Eugene Klein. His interest in experimental surgery is shown by his donations of research laboratories to the Mount Sinai Hospital and New York University.

Dr. Berg contributed to surgical literature in his younger years, but it is unfortunate that his vast experience of later years was not recorded. His contributions were excellent and showed the wide field of the general surgeon of his day. They included the treatment of exudative peritonitis; retroduodenal choledochotomy for the removal of impacted calculi in the retroduodenal and papillary portions of the common duct; the surgical treatment of cholelithiasis; the ligation of the splenic artery for purpura hemorrhagica; operative removal of a tumor of the Gasserian ganglion; the operative treatment of brain abscess; a radical operation for malignant neoplasm of the urinary bladder; the operative cure of malignant hypernephroma of the kidney. The only publication of his later years was the review of 516 operations for ulcer of the stomach and duodenum and gastrojejunal and jejunal ulcers.

One phase of Dr. Berg's work which has been almost completely overlooked was his diagnostic ability, perhaps because a surgeon's technical skill is always more dramatic. In 1905 his work on surgical diagnosis was published in book form. This memoir is aptly ended in the words of one of the reviewers of this book: "Dr. Berg is exceptionally well qualified to furnish a most practical and useful book, by reason of the fact that the surgical service of one of the largest and most perfectly appointed hospitals is and has been for years directly under his observation. The wide range of his experience and the broadness and accuracy of his knowledge are clearly reflected in the completeness and precision of this manual."

ERNEST E. ARNHEIM

## SCIENTIFIC RESEARCH IN MODERN HOSPITAL PRACTICE

GEORGE BAEHR, M.D.

With this memorial volume, we find it difficult to honor Dr. Albert Ashton Berg adequately for the lives which he has saved during the last fifty years through his great surgical skill could populate a large city.

Shortly before his death, the Hospital was made the recipient of a generous gift of a new research building by this devoted member of the staff in appreciation of its past scientific achievements and as an aid to scientific progress in the years to come. It is indeed paradoxical that the Hospital should again be indebted to a man to whom it already owes so much. To those of us who were his friends, associates, or students during his half century of service to the Hospital, the Berg Research Building will be a reminder of his great talents. To others who come after us and who will be so fortunate as to enjoy the research facilities that he has provided, it will perpetuate the memory of one of the greatest surgeons the world has ever known, whose vision was focussed on the medical horizon.

Our Hospital was established 96 years ago, long before the beginning of the golden era of medical science through which we are now passing. During the first fifty years of its history, when the basic medical sciences were still rudimentary, eminent clinicians and surgeons of the Hospital's staff were able to uncover some of the early mysteries of clinical diagnosis merely by careful methods of observation. Largely without the aid of instruments of precision, their clinical acumen enabled them to differentiate between numerous diseases which had previously been obscure or unknown.

Toward the end of the last century, the rapidly developing sciences of pathology, bacteriology, and biochemistry provided a new foundation for modern clinical medicine. Members of the clinical staff in that period visited the great European centers of learning and, on their return, they established new scientific disciplines in primitive laboratories in our Hospital. For several decades they conducted and developed these laboratories for the basic sciences while carrying on their routine clinical responsibilities on the wards and their private practice. From these early endeavors came a number of outstanding scientific contributions of national and even international importance on diseases such as subacute bacterial endocarditis, Brill's disease, Gaucher's disease, thromboangiitis obliterans, tubal sterility, regional ileitis, and on the surgery for peptic ulcer.

By 1926 the scientific laboratories of the Hospital had grown to such size and scope that they required full-time experts for their direction. Although now relieved of routine laboratory responsibilities by the appointment of full-time laboratory chiefs, some members of the clinical staff continued to carry on research in the central laboratories. In recent years clinicians experienced increasing difficulty in salvaging enough time from private practice and routine ward duties to participate seriously in research. This was due in part to the physical

separation of the central laboratories from the clinical services and the absence of full-time scientific leadership on any of the clinical divisions of the Hospital.

Before the onset of the Second World War it had become evident that the new order was seriously impeding the full professional and scientific development of the younger members of the clinical staff. The extraordinarily rapid growth of the medical sciences, to which biophysics and electronics were now added, and their direct application to problems of diagnosis and treatment of the sick, had made it mandatory to provide the clinicians with laboratory work benches close to their wards. It had also become necessary to train young clinicians of ability in the newly developing branches of medical science, not only in our own laboratories but in other educational and scientific institutions.

Accordingly, a Research Administrative Committee was designated for these purposes which includes representatives of the Board of Trustees, the central laboratories, and the major clinical services. In March 1944, a full-time Director of Clinical Research was appointed to administer the program. Upon his recommendation, new laboratories for clinical research were established adjacent to the medical and pediatric wards, on the sixth floor of the Administration Building and the medical pavilions and in the Laboratory Annex Building. Plans were completed for a new central laboratory building and for the Berg Research Building, and their construction is now under way.

With the aid of fellowships and grants from the Sara Welt Fund, from other generous individuals, and from philanthropic foundations, many young members of the staff have been given one or more years of special training in various centers of scientific research throughout the country. Upon completion of their training, these men have then been provided with laboratory space and opportunities to employ their scientific skills in collaboration with other workers organized as co-ordinated teams of investigators in fields such as endocrinology, cardiovascular and renal physiology, gastrointestinal physiology, nutrition chemistry, physiological hematology, immunochemistry, and clinical research with radioactive isotopes. New project applications as well as progress reports are now reviewed in detail monthly by the Research Administrative Committee, and all projects, if approved by the Committee, are thereafter aided and supervised jointly by the Director of Clinical Research and the chief of the laboratory or clinical service in whose field the project may lie.

The budgeted expenditures for laboratory and clinical research now exceed \$400,000 a year. Of this sum, more than half is defrayed by grants received by the Hospital for the support of specific research projects from the U. S. Public Health Service, the Army Research Board, the Atomic Energy Commission, the pharmaceutical and the food industries, the American Cancer Society, the American Heart Association, the Life Insurance Medical Research Fund, and from several of the large philanthropic foundations. Many research fellowships have come from similar sources, as well as from individual donors. It is now evident that continued support for research from sources outside the Hospital can be anticipated in the future, provided more adequate facilities for research can be made available, and provided the donors can be assured of competent full-time direction in each

of the major branches of clinical investigation. Funds are urgently required by the Hospital to meet these requirements.

In addition to a large number of scientific articles by members of the staff, some of outstanding importance, volumes on Diseases of the Adrenals and Diseases of the Heart have recently been published which are generally recognized as standard works in their respective fields. Aside from such direct results of scientific research, one of the most significant indirect benefits derives from the fact that clinical investigators constantly alert the staff of the Hospital on the newest developments in medicine. In each of their respective fields of science, they contribute their newly acquired information and experience to the common pool of knowledge and keep the entire staff abreast of these stirring times. This is especially evident in such work as the application of radioactive isotopes to the diagnosis and treatment of disease, the study of antibiotic drugs, the use of cortisone and ACTH for the control of the diseases of collagen, and the physiological diagnosis and surgical care of persons with congenital heart disease, new fields in which our Hospital is recognized as one of the primary centers of research.

We take pride in the flowering of the scientific spirit throughout the Hospital, especially during the five years since the close of the recent war. It gives us a still greater sense of satisfaction, however, to be able to report that this has been accompanied by a growing spirit of humanity, an ever-deepening concern of the clinical staff with the welfare and happiness of our patients. Throughout the Hospital we sense a greater awareness of the role of human behavior and of environmental influences in the development and the arrest of illness. The clinical study of the whole man is not being obscured by overly intense scientific concentration upon any one segment of his disease problem. This is the spirit of research of which Dr. Berg would have approved.

425 Avenue of the Americas  
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## SOME OF THE PRINCIPLES AND METHODS CONTRIBUTED BY THE SERVICE OF DR. A. A. BERG

LEON GINZBURG, M.D.\*

As the trend towards specialization within the field of general surgery began to be apparent in 1914, the grouping of certain specific surgical conditions under the direction of a single attending surgeon was initiated at the Mt. Sinai Hospital. The wisdom and foresight of this move, which permitted a more intense and concentrated study of various branches of surgery, has since then been amply proven. To Dr. A. A. Berg was assigned the surgery of the gastro-intestinal tract. During the subsequent twenty years, his tremendous capacity for work, his boldness and resolution, his extraordinary operative skill and his refusal to remain on the accepted path, had brought his service to an enviable position in the field of abdominal surgery. The most significant studies from his clinic were in the fields of gastroduodenal and jejunal ulcers. Other important contributions were made to the subjects of colonic, and more particularly, rectal and recto-sigmoidal carcinoma. Moreover, it was from studies made on his service based on his clinical and operative material that the concept of Regional Enteritis as a clinical entity emerged.

### GASTRODUODENAL AND JEJUNAL ULCERS

When the service for gastro-intestinal surgery was first organized the commonly recommended surgical procedures for duodenal ulcer were gastro-enterostomy and pyloroplasty. The latter procedure was found to be technically applicable only in a relatively small number of cases and regardless of its other merits or demerits never found wide application. Gastro-enterostomy, however, steadily gained favor throughout the United States and it was commonly believed that a definitive operative approach to the treatment of duodenal ulcer had been attained. The end results were considered excellent and the incidence of post-operative stomal ulceration was generally reported to be between 0.5 to 2 per cent.

Direct first hand investigation of the results of the service's own gastro-enterostomies, at the follow-up clinic personally conducted by Dr. Berg, soon began to cast doubt upon the supposed effectiveness of this procedure in the management of duodenal ulcer. Radiological and operative studies upon patients suffering from recurrent symptoms revealed the incidence of gastrojejunal ulcer to be very much higher than the percentage previously indicated.

Lewisohn in 1925 reported that the frequency of gastrojejunal ulcer following gastro-enterostomy for duodenal ulcer performed on the service of Dr. Berg was 34 per cent. This article had an explosive effect in both medical and surgical circles, and rudely jarred the complacent satisfaction with which the employment of gastro-enterostomy had come to be regarded. A prolonged and widespread controversy developed as to the relative value of gastrectomy and gastro-enteros-

\* Director of Surgery, Beth Israel Hospital, New York City.

tomy, which at times reached highly acrimonious levels. In the beginning, the opponents of the more radical procedure overwhelmingly outnumbered its supporters, who by the way, in this country, constituted only a handful. In spite of this, the Mount Sinai group persisted in the continuation of what they conceived to be the correct course. Slowly and almost imperceptibly, the tide turned, and an increasing number of surgeons and surgical clinics came to regard partial gastrectomy as the more satisfactory procedure. Today there are likely very few surgical centers where gastro-enterostomy is still considered the operation of choice for active duodenal ulcers.

Observation at operation and the availability for study of resected specimens, comprising stomach, stoma and duodenum *en bloc*, threw new light on the shortcomings of gastro-enterostomy. Gastrojejunal ulcer had to a large extent been treated as though it were a local complication requiring local corrective measures. Instead, these studies showed that it was the result of the same factors originally producing duodenal ulcer but now acting at a new and surgically created "*locus minoris resistantialis*". With this in mind, the treatment of stomal ulceration logically became the same as that best calculated to combat the original duodenal ulcer.

Thus, it was repeatedly noted that excision of an active stomal ulcer followed by plastic repair led to renewed ulceration at that site. When stomata, the seat of ulceration were disconnected, and another gastro-enterostomy performed, ulceration was likely to occur at the new one. In the presence of a double gastro-enterostomy, the ulcer was noted on two occasions to develop in the one best located from the stand-point of function. Where the gastro-enterostomy functioned poorly, as from malposition, or too small an orifice, jejunal ulceration appeared to be uncommon; but the *original duodenal* ulcer appeared *unaffected*. Well functioning stomata which caused disappearance of the original duodenal ulcer were, however, apparently more susceptible to the development of stomal ulceration. Patients with ulcer of the lesser curvature of the *stomach* appeared not to develop stomal ulcers. But here again the original ulcer appeared to be unaffected.

Most significant were the phenomena noted when active jejunal ulcer was treated by simply disconnecting the stoma. In a number of such instances, the old duodenal ulcer which had been found in a condition of apparent healing, became reactivated. Performance of a new gastro-enterostomy again resulted in quiescence of the duodenal ulcer with the development of another active jejunal ulcer. It seemed fair to conclude, therefore, that in the presence of an active tendency to ulcer formation, gastro-enterostomy would frequently serve only to transfer the site of the ulcer rather than to affect the basic disease processes. This was borne out by the examination of the duodenum in cases where gastro-jejunosomy had produced retrogression of the original duodenal ulcer. Signs of intramural fibrosis, which is the only morphological evidence of that type of healing which accompanies subsidence "or burning out" of the ulcer tendency, were not conspicuously present.

As the result of these observations, the operation of gastro-enterostomy was given up, except for stenosis due to fibrosis, and unaccompanied by evidence of

ulcer activity; and also for those cases where gastrectomy was not feasible either for local or general reasons. From 1923 partial gastrectomy was the operation of choice for primary and secondary gastroduodenal and jejunal ulcers.

The results from this time on proved to be vastly superior to those obtained by previous procedures. However, continuation of careful followup studies showed that partial gastrectomy also was not the final answer to the problem. The superior results of this procedure had been attributed partly to the fact that it removed the antral gastritis which was considered to be linked to the production of duodenal ulcer. Moreover, it was believed that these results were due to the production either of an anacid or subacid condition of the gastric secretion. In *gastric* ulcer of the lesser curvature this desideratum was found to be almost invariably obtained. In duodenal ulcer it was *not* reached in approximately one-third of the cases. Jejunal ulcer was found to develop in approximately 7 per cent of the cases. In a few cases the disease appeared to be intractable, new jejunal ulcers developing even after secondary extensive resections, leaving only a small stump of the stomach. The possibility of other approaches to this problem had to be explored.

Speculation had long been rife concerning the relationship of vagus action to peptic ulceration. Dr. Berg had for some time been interested in this phase of the problem. The late Dr. Eugene Klein, a member of his service, had conducted animal experimentation to study the effects of vagus section on gastric physiology and the role that it might play in the management of the ulcer problem. This was being studied at a time when little was known about the effects on the gastrointestinal tract of complete bilateral supra or infradiaphragmatic vagus section in man. There was, therefore, an understandable hesitancy on the part of Dr. Berg to perform bilateral vagus section, and accordingly he experimented with resection of the anterior vagus nerve by sectioning its branches after it had divided, performing this procedure simultaneously with gastrectomy.

While the work was still in its developmental state, Dr. Berg retired from active ward service and further efforts along this line were permitted to lapse for a while. But the seeds thus planted did eventually come to full fruition at The Mount Sinai Hospital. In the course of resections for esophageal carcinoma Dr. Garlock noted that the inevitable bilateral vagus sections produced no deleterious clinical effect on gastrointestinal function. Dr. Colp who took over the gastric division of the Gastrointestinal Service revived the interest on the effect of vagotomy upon peptic ulcer, and in 1939 he employed the transthoracic approach for a division of both vagi in 2 patients suffering from recurrent ulceration following gastrectomy for duodenal ulcer. The division of right and left main vagus trunks was accomplished just above the diaphragm.\*

#### OPERATIVE MANAGEMENT OF DUODENAL ULCER

The various supportive and auxiliary measures which play so prominent a role in surgery today were only in a relatively primitive state of development in 1923. In the absence of blood banks, blood was not available for transfusion in

\* These were the first recorded cases of bilateral transthoracic vagotomy for gastrojejunal ulcer.

the quantities and the ease with which it can be obtained today. The citrate transfusion, though already well defined, did not stand in the high favor which it does today. The type of transfusion preferred at the Mount Sinai Hospital at that time, was the direct Unger method, which made transfusion on the operating table highly impracticable. The standardization of solutions of glucose for intravenous use had also not been developed to a point, where it could be given without danger of a pyrogenic reaction. The only fluid that could safely be administered parenterally was normal saline which was given either by hypodermoclysis or intravenously. Anesthesia also had not reached the state of development which we know today. The only anesthetic gas available at that time was nitrous oxide and oxygen. It was soon found that in these extensive upper abdominal operations the use of this agent and ether was often followed by the development of severe forms of postoperative pneumonia. There were no sulfonamides or antibiotics available to combat these serious complications. In an effort to diminish their incidence and lessen their severity, local anesthesia came into use. At first this consisted mainly of abdominal wall block with novocaine. The absence of relaxation increased the technical difficulties of the procedure, and especially in complicated cases, the traction upon the duodenum and the retraction of the abdominal wall necessary for exposure, made the operation an ordeal for both patient and surgeon. The year 1928 was marked by a revival of the use of spinal anesthesia for abdominal cases and this method of anesthesia became the one of choice.

The operative procedures adopted by Dr. Berg consisted of both variable and constant features. The variables were the result of the pathological—anatomical alterations engendered by the underlying disease and encountered at the operating table. These were managed in a fashion best suited to the individual case. The constant elements were those used in the actual resection after mobilization had been achieved, and in the restoration of gastro-intestinal continuity. The final standard procedure that Dr. Berg employed for the treatment of ulcer was arrived at only after experimentation with other variants. It consisted of a resection of the distal two-thirds of the stomach, the resection being carried into the duodenum to a point *distal* to the site of the ulcer, except in ulcers involving the second portion of the duodenum. Continuity was re-established by a posterior, retrocolic, end to side implantation of the lower two-thirds of the stomach, into a loop of jejunum a few inches distal to the fossa of Treitz, after having first closed the upper one-third of the cut end of the stomach. Dr. Berg arrived at this method independently and for a while thought that it was original. Research into the German surgical literature revealed that it had been previously described by Hofmeister. Dr. Berg, however, was largely responsible for popularizing its use in this country.

The operation was performed through a median epigastric incision running from the ensiform process to the umbilicus. In the event that more room was required the umbilicus was excised. These patients, frequently in a debilitated and malnourished condition, who were likely to subject the wound to considerable stress as the result of coughing, vomiting or hiccuping were likely candidates for wound disruption. Dr. Berg departed early from the standard closure



in layers with catgut and in the median incision substituted the use of heavy through and through silk sutures, which took a small bite of skin and increasingly larger bites of facia and peritoneum. Though this method produced wounds not exactly remarkable aesthetically, it practically eliminated post-operative eviceration. This median incision was originally not very popular with most operators, but an increasing number of gastric surgeons have come to adopt it because of the ease of entry, its superiority for overall exposure and the relative ease and security of closure by various through and through types of sutures.

On entering the abdomen the region of the duodenum was exposed by retraction of the liver and the right side of the wound. Adhesions of the liver, the fundus or ampulla of the gall bladder and the omentum and colon were divided. This dissection, which at times was fairly extensive, was continued until the anterior face of the duodenum and its upper and lower borders were exposed, well down into the second part. The relation of the ulcer and its degree of penetration onto the head of the pancreas and the gastrohepatic omentum was then determined and the decision reached as to whether the lesion was safely resectable. Parenthetically it may be stated that only rarely was this answered in the negative. The actual resection was begun proximally by securing the coronary vessels of the stomach a few inches proximal to the re-entrant angle. The lesser sac was then entered, the stomach drawn forward and the left gastro-epiploic vessels secured. The gastro-colic ligament was then divided distal to the arch of this vessel for a short distance. The lesser sac was then exposed and the almost invariable adhesions of the superior surface of the transverse mesocolon to the posterior wall of the stomach were divided. The mesocolon was then wiped gently downward carrying the middle colic vessels away from the operative field, and out of danger. Adhesions of the hepatic flexure area of the colon were then dissected and the colon pushed downward. Section of the gastrocolic omentum was continued to the point, an inch or so proximal to the pylorus, where the right gastro-epiploic vessels pass upward and backward to reach the head of the pancreas. At this point they were secured and divided. After ligation of all previous secured vessels, the colon and gastrocolic omentum were reduced into the abdomen. The pyloric vessels were then secured and divided. The abdominal wall was now carefully protected by pads which served also to isolate the operative field from the rest of the abdomen. Rubber covered clamps were then applied to the stomach at the elected site of transection, and the anterior gastric wall divided down to the submucosa. The numerous intragastric vessels running parallel with the long axis of the stomach were exposed and secured on the proximal side with mosquito clamps. The mucosa was then divided exposing the mucosa of the posterior wall of the stomach. This was then carefully incised to expose and secure the vessels running beneath it. The muscular and serosal coats of the stomach were then divided. The cut edge of the stomach was then covered with pads and towels and attention directed to the dissection of the duodenum.

Using the divided stomach for traction, the vessels entering the duodenum at its upper and lower borders and posterior wall were carefully dissected away. The dissection was continued until the duodenum was sufficiently mobilized to

permit safe closure or until a sealed-off penetration against the head of the pancreas was encountered. In the latter case the bed of the ulcer penetration was left in situ, and the dissection of the distal area carried far enough to permit the posterior wall to be sutured. The duodenum was then cut across.

For the competent closure of the duodenal stump, Dr. Berg depended mainly on his first layer of closure, which was a running connel stitch of fine chromic catgut. This was very accurately passed and meticulous inversion of the edges practiced. The suture was commenced at the upper angle of the duodenum and carried downward. In complicated cases seldom was there enough posterior wall to permit the passage of a second layer between anterior and posterior duodenal wall. The suture line was reenforced by sewing the anterior surface of the duodenum to the "capsule" of the pancreas (in reality thickened and fibrotic peritoneum covering the anterior face of the pancreas and resulting from reaction to the penetrating or perforating duodenal ulcer). This thickened tissue was found to hold sutures well and to serve as a good base into which the first suture line could be turned. The duodenal stump was then further reenforced by sewing the remnants of the gastrohepatic gastrocolic omentum to the anterior wall of the duodenum. Where closure of the duodenum stump had presented great difficulty, a rubber tube drain was placed in the subhepatic space in the vicinity of but not in direct juxta-position to the stump.

The field was then shifted to the cut end of the stomach and the intra-gastric vessels previously secured were ligated. The upper one-third of the stomach was closed with a running connel stitch of catgut. The transverse colon was then raised and a vertical incision made in a free space between the arcades of the middle colic vessels. A loop of jejunum a few inches distal to the fossa of Treitz was brought up through this opening. The left leaf of the mesocolon was then sutured to the posterior wall of the stomach, a rubber covered gastric clamp applied to the jejunum and an anastomosis performed between it and the lower cut edge of the stomach, in such a manner that the afferent or proximal loop was at the upper border, and the efferent or distal loop at the lower border. The anastomosis was accomplished in the standard fashion, using a running Lembert stitch of linen for the outer most layer and a running catgut stitch for the posterior layer. This latter was passed as a lock stitch on the posterior wall of the anastomosis and as a connel stitch on the anterior surface. When the anastomosis was completed the initial suture line at the upper angle of the stomach was reenforced by a sero-muscular stitch of linen. The anastomosis was then reduced below the transverse mesocolon and the right leaf of the mesocolon sewn to the anterior wall of the stump of the stomach.

The operation for *gastrojejunal ulcer* may be a formidable procedure even under favorable circumstances. In a great many of the patients who were finally subjected to gastrectomy in the early days, these difficulties were increased by the fact that many of them passed through a series of so-called conservative operations. These included operations for previous acute perforations, gastro-enterostomies, disconnections of gastro-enterostomies, multiple gastro-enterostomies and plastics upon gastro-enterostomies. In addition to these there were other instances in which surgeons had performed lysis of adhesions and cholecystec-

tomies, the latter for what was apparently assumed to be chronic pancreatitis. Incidentally, the marked induration in such cases were usually found to be due to perforating posterior duodenal ulcers. Patients with two or three previous operations were not uncommon. The writer recollects one who had been subjected to eight previous abdominal procedures. In these cases where the difficulties were at times staggering, Dr. Berg was truly the surgical virtuoso. Entering the abdomen without injuring a hollow viscus, was in itself somewhat of a feat. When this had been accomplished, at times nothing could be seen but a solid sheet of adhesions which enswathed the upper abdominal viscera, obliterated almost all landmarks and made orientation extremely difficult. By traction upon the abdominal wall and by maintenance of constant tension upon the viscera by the assistants, planes of cleavage were gradually defined and omentum colon and stomach separated from the parietal peritoneum. When the transverse colon had been defined it was raised up out of the wound and the under-surface of the transverse mesocolon exposed. It was further mobilized by sharp dissection, and adhesions of small intestinal loops freed, until the gastro-enteric stoma and its afferent and efferent loops were exposed. When these showed evidences of disease, the operation was proceeded with. If not, the duodenum was now exposed, for not infrequently, a malfunctioning or poorly placed stoma had resulted in the persistence of the original duodenal ulcer.

In either event the transverse mesocolon was separated from its attachments to the stomach where it had been sutured at the time of the gastro-enterostomy. This was done with great care, a careful watch being kept for branches of the middle colic artery. When this had been completely or almost completely freed, the stomach was mobilized in the manner described above and the jejunal loops entering into the anastomosis brought up above the mesocolon. At this time the further course was determined by the size of the stoma and the extent of the inflammatory reaction around it. If the stoma was large, and inflammation severe, the segment of bowel was resected and left in situ on the stomach. Reconstruction of intestinal continuity was accomplished by a two layer end to end anastomosis between the jejunal loops. In patients where a very short loop had been used for the gastro-enterostomy this part of the procedure was at times very trying.

In cases where the stoma was small or shrunken, the jejunal part of the anastomosis could at times be dissected away, and closed transversely. The use of this simpler procedure was limited by the fact that any stenosis at this point would result in back pressure by biliary and pancreatic secretions, which would endanger the competency of the duodenal stump left by the simultaneously performed gastrectomy. A new gastro-enteric anastomosis was accomplished distal to the site of disconnection and the defect in the transverse mesocolon utilized for the performance of the posterior retrocolic type of anastomosis.

#### CARCINOMA OF THE COLON

In the surgery of carcinoma of the colon, the methods used for resection had been fairly well defined by the time that Dr. Berg took over the service for gastro-



enterological surgery. His contributions in this field were mainly refinements of technique and the extension of operability, until in his hands relatively few cases were considered inoperable because of local extension. He favored resection and anastomosis rather than the Mikulicz procedure which he deemed insufficiently radical. He reserved this latter procedure for patients in poor condition. Compared to the colonic surgeon of today, he was handicapped by the absence of drugs to control the bacterial flora of the bowel, the absence of per-oral intestinal intubation, in addition to the lack of supportive and anti-infectious measures mentioned above. He recognized the importance of intestinal decompression prior to operation, and attempted to effect it by the only means at his control, to wit, the use of non-residue diets, laxatives and enemata. When such decompression proved not to be feasible a cecostomy was performed. He had little faith in the efficacy of tube cecostomy but instead exteriorized a segment of cecum opposite the ileo-cecal valve in order to secure diversion, as well as adequate drainage of intestinal contents. In cases of right sided colonic obstruction an ileo-sigmoidostomy with exclusion was done as a first stage procedure.

Most colonic resections, however, were performed in one stage. In the early days of the service colonic resections could not be undertaken with the assurance of success that can be assumed today. Diagnosis was not as accurate as it is today and the patients came to operation at a more advanced stage of the disease and in poorer condition. Resection in order to be at all tolerated had to be expeditious, atraumatic and conducted with a minimum of bleeding and contamination. At a time when many surgeons prided themselves on the shortness of the incisions through which they worked, those of Dr. Berg were always adequate enough to provide for performance under direct vision and for maneuverability without undue struggle. The operative field was walled off from the rest of the abdominal cavity and the abdominal wall protected by the judicious use of moist pads and the skillful placing of retaining retractors. In order to reduce the possibility of contamination, a strict aseptic technique was developed. The involved loop was exteriorized before any operative measures were performed upon it. The entire area around it was again protected by pads and towels. As soon as the bowel was opened a special tray of instruments was placed on the operating table which the instrumentaire handled only sparsely and then only by the "no touch" technique. When the unclean part of the procedure had been completed, linens, instruments and gloves were changed.

Dr. Berg favored the open anastomosis. It enabled him to judge directly the sufficiency of the vascular supply of the segments to be united, and left no crushed and necrotic diaphragm to provide a nidus for infection. Whenever possible, as in ileo-colic resections or in patients with redundant transverse or sigmoid colon, he preferred a lateral anastomosis. In the others, which, of course, constituted the great majority, a very meticulous end to end suture was performed. In both he used an outer layer of fine linen, passed continuously in the lateral, and as interrupted sutures in the end to end type. The inner layers were a fine chromicized catgut which he used as a running lock stitch posteriorly and a Connel suture anteriorly.



For lesions located between the cecum and right transverse colon, a resection of the terminal 6 to 8 inches of ileum extending around to the right one-third of the transverse colon was performed. The ileo-colic, the right colic and the right branch of the middle colic vessels were ligated and the entire mesocolon with its glandular elements was removed. The ureter and second and third parts of the duodenum were always exposed. Continuity was re-established by a iso-peristaltic lateral anastomosis. The cut edges of the divided mesentery of the terminal ileum and the transverse colon were carefully sutured and the retro-colic space reperitonealized. Drains were placed into the upper portion of the retro-peritoneal space.

For neoplasms of the transverse colon the resection was carried as widely distal on both sides as was compatible with the performance of an anastomosis without tension. To attain this end the hepatic and splenic flexures were frequently mobilized and extensive resection of the gastro-colic omentum and great omentum carried out.

Lesions of the splenic flexure were usually approached through a left subcostal incision extending into the flank and the resection carried from the left transverse colon to the sigmoid with wide removal of the accompanying mesocolon. The same procedure was used for carcinoma of the descending colon.

For carcinoma in the sigmoid a block resection of mesentery and sigmoid was done continuity being restored by end to end anastomosis, except in cases where an unusually redundant sigmoid permitted the use of a lateral anastomosis.

At present operations of this scope and magnitude are daily carried to a successful conclusion by surgeons still in the formal training period of their careers. This in itself is a tribute to the thoroughness with which the pioneer surgeons in this field, of whom Dr. Berg was emphatically one, accomplished their task. There is nothing so indicative of progress in surgery as when the "tours de force" of yesterday have become the commonplaces of today.

#### CARCINOMA OF THE RECTUM AND RECTO-SIGMOID

For carcinoma of the rectum and recto-sigmoid Dr. Berg used a variety of procedures. The old controversy centering about the question of preserving anal continence was debated as widely in his day as it is now. Dr. Berg held to the belief that in certain types of malignancy of the upper rectum and recto-sigmoid, the anal sphincter could be saved without unduly imperiling the end result. For carcinoma of the recto-sigmoid above the peritoneal level, he used a type of anterior resection. For carcinoma of the recto-sigmoid and upper rectum, he used a combined procedure of abdominal mobilization followed by immediate posterior resection with a pre-sacral extra-peritoneal anastomosis performed from below. For lesions of the middle and lower rectum, he ordinarily used an abdomino-perineal resection which he credited to Quenu, a French surgeon, of the turn of the century. The same procedure is usually referred to in the English and American literature as the Miles operation. For lesions of the rectum in patients who because of age or poor condition, were considered unsuitable for a combined procedure, a posterior resection with formation of a permanent sacral anus was performed, the so-called Kraske operation. In some instances he pur-

sued the mobilization from below well up into the sigmoid and performed both resection and anastomosis from below.

#### ABDOMINO-PERINEAL RESECTION

A left para-median rectus incision was used extending from symphysis to umbilicus. With the patient in a high Trendelenburg position, the small intestine was packed away into the upper abdomen, a self retaining retractor was inserted, the center-piece of which contrary to general usage, Dr. Berg placed at the upper angle of the wound in order to help keep the upper abdominal contents out of the field. The bottom of the pelvis was exposed by retracting bladder or uterus with long bladed retractors. A U-shaped incision was made in the peritoneum, lateral to the recto-sigmoid on both sides and carried anteriorly through the recto-vesicle or recto-vaginal peritoneal reflection. The plane between the seminal vesicles and bladder were defined and the rectum separated from them. The presacral space was then entered from above and the posterior rectal wall freed down to the levator ani. When the mobilized rectum was now drawn up into the wound, the superior hemorrhoidal vessels stood out as a distinct chord subtending the arc of the rectum and sigmoid. By this maneuver it was drawn well away from the region of the left ureter. It was divided above the level of the sacral-promontory, following which the sigmoid mesentery was divided at right angles to the bowel, at a level which would permit exteriorization of the proximal portion without tension. The sigmoid was then divided between two heavy silk sutures the ends being carbolized. The proximal one was brought out at the upper angle of the wound to form a permanent colostomy and the lower end wrapped in gauze and pushed down in the sacral hollow. The pelvic floor was then reconstructed by sewing together the previously divided pelvic peritoneum. Following closure of the abdominal wound the patient was turned into the lateral or Sims position with the left side up. The anus was closed by purse string suture, a circumferential incision was then made a few inches around it and carried down through the fat of the ischio-rectal fossa. The incision was then extended upward and slightly to the left of the coccyx and lower sacral segment. The coccyx was excised and the levator ani muscles divided well out from the rectum. The lower lateral attachments were then divided and the previously mobilized recto-sigmoid drawn through the wound. This exposed the anterior surface of the rectum which was then dissected away from the prostate and membranous urethra. The recto-vesicle fascia was incised on either side and the dissection carried downward, the final step being dissection away from triangular ligament and the fixed point of the perineum. The large space in the sacral hollow was drained with a number of median packings and a rubber tube which were brought out to the lower angle of the wound. Closure was confined to the upper portion of the skin incision.

#### ONE STAGE COMBINED PROCTO-SIGMOIDAL RESECTION IN CONTINUITY

This procedure was apparently unique for many years with Dr. Berg and some of the men whom he trained. The author saw no references to, or descriptions of, this procedure, in the American literature until a few years ago. When the author

first came to Mt. Sinai as an interne thirty years ago, this procedure was being employed by Dr. Berg in a standardized fashion. It has the advantages over anterior resection of allowing removal of a greater segment of lower rectum. It has the advantage over the pull-through operation of not in any way compromising the sphincter. It was an intervention of considerable magnitude, requiring three changes in the position of the patient, and likely to be accompanied by shock if not accomplished with dispatch and facility.

The abdominal portion of the operation was carried out in a manner similar to that described for abdomino-perineal resection. The superior hemorrhoidal artery was tied somewhat higher and the sigmoid mesentery divided more obliquely downward to permit of utilization of maximum sigmoid length. The vessels immediately adjacent to the bowel were cut before they were clamped in order to determine the competency of the blood supply. At the point of proposed division of the sigmoid a tie of umbilical tape was placed loosely around the bowel. The mobilized bowel was then replaced in the pelvis and the abdomen provisionally closed with heavy through and through silk sutures. With the patient in the Sims position an incision was made along the left border of the sacrum and coccyx to a point just below the coccyx, where it was curved transversely to the opposite side, a sort of hockey stick incision. The sacral origin of the gluteus maximus and the lower portion of the sacro-sciatic ligament were divided, the large branches of the inferior gluteal artery being secured. To provide more room the lower sacral segment was at times divided with a chisel, in addition to excising the coccyx. The upper posterior portion of the levatores ani were divided and the previously mobilized bowel brought out through the posterior wound, until the point of previously marked competent blood supply was reached. The dissection was now carried anteriorly separating the rectum from the prostate and further mobilizing the lower segment by dividing the recto-vesicle fascia. The involved bowel was then resected between clamps, rubber covered ones being used above and if possible below. The anterior portion of the anastomosis i.e. the portion adjacent to the prostate or vagina were united with interrupted chromic catgut sutures going through all layers of the bowel. Posteriorly a running suture of chromic passed in the Connel fashion was used, this being reenforced with interrupted Lambert type sutures of chromic passed individually. Experience showed that anteriorly, where the suture line could be buttressed against the prostate or vagina, dehiscence rarely occurred. Posteriorly, where there was an inevitable dead space some separation of the suture line was likely to occur. Wide drainage was provided by a number of packings and a tube introduced well into the pre-sacral space.

After complete change of gowns, gloves, instruments and linen, the patient was again turned on his back and the abdominal cavity reentered. This permitted a careful peritonealization of the pelvic floor around the transposed sigmoid. As a final step a tube cecostomy was performed, the tube being drawn out through a small McBurney incision.

#### ANTERIOR RESECTION

This procedure was used when the neoplasm was at a level which permitted its removal distally without the necessity of mobilizing the sub-peritoneal pre-

sacral portion of the rectum. Instead of performing his usual end to end type of anastomosis, Dr. Berg employed an invaginating or telescoping type of procedure. A number of sutures were passed through the proximal loop near its cut end and tied to a sound. The sound was then passed through the distal segment and out through the anus. There it was grasped by an assistant who drew it and the attached sutures outside of the anus. The upper segment was guided into the lower for a few inches. A series of Lembert-like sutures were then introduced to unite the two segments. Drains were inserted to the region of the anastomosis and brought out through the lower angle of the wound and a tube cecostomy performed.

#### POSTERIOR RESECTION

These were performed by Dr. Berg in the same manner as described in the posterior part of the abdomino-perineal and proctosigmoid resection and continuity.

#### REGIONAL ILEITIS

The name of Dr. Berg is not usually associated with this condition. There is a certain element of injustice in this, for as a matter of fact, the original studies of this disease as well as other granulomata of the bowel, was almost entirely carried out on specimens which he had resected both on the ward service and in his private practice. The interest of one of the co-authors of the original paper on ileitis (the present writer) was directed to the inflammatory surgical lesions of the bowel by Dr. Berg. In the course of an operation for late intestinal stenosis following strangulated hernia, at which the author was assisting, he remarked that the subject of inflammatory lesions of the bowel could stand considerable clarification. He also intimated that it would be a good idea for a young surgeon to pursue such studies. A collection of specimens of resected inflammatory lesions of the bowel was undertaken in conjunction with Dr. G. D. Oppenheimer at that time working in the department of surgical pathology. So extensive was the operative material of Dr. Berg that within a few years a fairly large collection of various types of intestinal granulomata had been accumulated and studied pathologically with the aid of Dr. Klemperer. The interest of Dr. Crohn had also been aroused by certain clinical observations upon patients of his own. Resection in these instances were also performed by Dr. Berg, and a combined study was made, as a result of which, the description of regional ileitis as a clinical entity emerged.

As is inevitable in diseases the nature of which is not well understood, the early cases of regional ileitis came to operation at an advanced stage. There were a fair number of them complicated by ileo-sigmoidal and ileo-colic fistulae as well as marked adhesions to the pelvis viscera and to other loops of small bowel. It required considerable fortitude to perform these extensive resections for an unknown condition, and great skill to bring them to a successful conclusion. Dr. Berg early realized that the lesion of terminal ileum was confined to the small bowel and did not carry resection to the transverse colon. Instead, he terminated it in the beginning of the ascending colon. It is also noteworthy that in cases



where technical difficulties and the magnitude of the operation forbade resection, Dr. Berg performed ileo-colostomy with exclusion and achieved good results. Four such cases were reported in the original article appearing in 1932. Also worth emphasizing is the fact that Dr. Berg at all times insisted that ileo-colostomy be accompanied by exclusion, achieved by complete division of the bowel at a point well proximal to the last visible evidence of the disease. He maintained that only in this way could the maximum beneficial effect be obtained upon the inflammatory lesion.

Later clinical and experimental reports in the literature have shown the wisdom of this procedure.

#### SUMMARY

In the foregoing the writer has only sketched the high lights of some of the contributions made by and the principles and methods employed by Dr. Berg and his service. The period covered is largely that from 1923 to 1934 when the author had the privilege of being a participant in the group as house officer and adjunct surgeon. Limitations of space prevented description of all the activities occurring during that period alone, in the detail which they merit. To chronicle adequately all of Dr. Berg's "labors in the vineyard" would be to write an important chapter in the history of the development of abdominal surgery in the United States.

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## TOWERING MEN OF MEDICINE

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The old adage that children should be seen and not heard ought to apply to garrulous old men who like to reminisce—but unfortunately doesn't. Hence in this volume to honor my friend, Dr. Albert A. Berg, I grasp the opportunity to look back upon the earlier days of medicine when there were certain Doctor Giants who attracted patients and doctors alike to the various institutions with which they were associated. Like the Massachusetts General, the Johns Hopkins, the Mayo Clinic, and other great medical centers, Mount Sinai had its full quota and should be proud.

Dr. Berg first attracted me and I recall the many visits when I stood at his elbow and marveled at his operative dexterity, the quick, precise way he did things and his supreme confidence. Mostly I came away disconsolate and vowing never to return. It was so different from the Hopkins School where Halsted advocated the slow, methodical way. But there was a lure and I always came back. Not only that, I brought others from Hopkins with me sort of to share my misery—as they did. Especially did Berg's beautiful gastrectomies arouse our envy. He could do two while we were doing one. The only comfort we took was the conviction that he was too radical and did too many. In the light of latter day happenings I am not so sure we were right. One thing, though, made us happy. Berg practiced in New York!

But there were compensations and we used to "wash that man Berg right out of our hair" (which we all had then) by visiting with the brilliant, quickwitted Libman. Even surgeons could be forgiven for taking in the show he always put on at rounds. And then came Richard Lewisohn with his epoch making exploits in blood transfusion, and the famed Isidor C. Rubin, with his tubal insufflation and gynecology.

Those were the days when the sick came to the outstanding Great Lights to be healed and the doctors came to learn. It's all changed now, due to better and more widespread education and rapidly advancing medical science. What with the antibiotics and other aids everybody "gets in the act" now, as Jimmy Durante would say. I know it's better this way; I know that the excellence of the hospital is the great magnet today and not the shining individual doctor, but the other was much more fun! It's like a lot of other things in this world, I suppose. First things must come first. In the days when people were afraid of hospitals it took the Great Giants to give them confidence. Mount Sinai and its staff of today and tomorrow might well say, "Our Towering Men were the equal of any."

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## Dr. A. A. BERG: AN APPRECIATION

LEOPOLD STIEGLITZ, M.D.

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It is just forty years since I had the good fortune to meet Dr. Berg. The very first case he operated on for me was myself, and it was a mere chance that brought us together. I was leaving my house to call on Dr. X to arrange for a herniotomy, as I had had a relapse after having been operated on the previous year, when I ran into Dr. Richard Lewisohn. In the course of conversation, I told him where I was going and he made the remark, "As long as you are going to be operated on by a Mount Sinai Surgeon, why not by the best one there?" When I asked whom he meant, he answered, "Why, Dr. A. A. Berg, of course." I took his advice and went to see Dr. Berg, who was most cordial and cooperative. I expressed the wish to have the operation done under local anaesthesia, and to be my own medical attendant after the operation; to both of these conditions he promptly agreed. That was my first contact with Dr. Berg.

Throughout the many years to follow, I found him always ready with his skill, and his friendship to assist me in my surgical cases, rich and poor alike. Day or night, and whatever other engagements he may have had, he was always willing to answer my call.

But, however much I valued his friendship, it was Dr. Berg's great skill, his excellent judgment at the operating table, that I valued most highly. It was because of this and a sacred obligation to my patients to provide them with the best, that he was the surgeon of my choice.

Most of the cases Dr. Berg operated on for me were abdominal, and a few of these stand out in my memory. One of them was the mother-in-law of a prominent physician who had been operated on by a gynecologist for what he diagnosed as an ovarian cyst, but which, to his surprise, turned out to be a malignant growth, necessitating a resection of the lower sigmoid, and the telescoping of the two ends of the intestine in order to reunite the cut gut. This caused a partial stricture, and thereafter the patient always had the greatest difficulty in moving her bowels. One day she could not move them at all, and quite naturally she called up her son-in-law for advice. He told her to take an enema, which she did. When not a drop of water returned, she became alarmed and sent for me. I found her in great pain, with her abdomen distended. I could feel the water splashing along the colon, especially along the ascending colon. Realizing that the patient had a complete obstruction of the bowel, I asked Dr. Berg to see her with me and, of course, invited her son-in-law to join us. This was in the evening, and when Dr. Berg suggested an immediate operation, the son-in-law was all for waiting until the following morning. But both, Dr. Berg and I realized the urgency of an immediate operation, and hence this was promptly carried out.

On opening the abdomen pretty freely, Dr. Berg lifted out the very much distended ascending colon, and through the transparent gut one could see the level of the water fluctuate. Working with his right hand, while he held the gut

in his left, he finally told his assistant, "Now you take hold of this." Almost instantly the distended gut burst, and the son-in-law, who was standing by, exclaimed, "There goes her last chance." Dr. Berg continued to work and completed his job. When we were leaving the operating room, I asked him whether he thought the patient had a chance after all the dirty fluid had poured into her belly. He answered, "She'll be all right. I expected that; so I protected the peritoneal cavity with sterile gauze and towels, and not a drop got in." The patient passed through a stormy convalescence but made a complete recovery and lived for years afterwards. This is the kind of work in which, in my experience, Dr. Berg was preeminent. He was absolutely at home in all abdominal work and I always thought he operated as though he had an eye at the tip of every finger.

I well remember one of the many appendectomies that he performed for me. A Frenchman whom I had never seen before sent for me, complaining of severe abdominal pain, which I found to be due to an acute appendix. I asked Dr. Berg to remove it that very day. On operating he found that the appendix was turned upwards towards the liver. At the sight of that, Dr. Berg remarked that the tip of the appendix might be gangrenous and that, if he tried to pull it down, the tip would break off and the patient would get a fatal peritonitis. I can still see him working gingerly along the appendix, clearing it from all adhesions and the mesentery, lifting it out and then remove it in the usual manner. And the tip of the appendix was gangrenous. Once more his great skill and experience saved a life.

Among the many appendectomies Dr. Berg performed for me, an empyema of the appendix was not a rare occurrence. My own little grandson, at the tender age of not quite three years, had an empyema of the appendix. Not once did such an appendix burst in the deft fingers of Dr. Berg. This is quite in contrast with my experience with another outstanding surgeon some thirty years ago, and serves well to explain why I selected Dr. Berg almost exclusively to do my operative work. One Sunday morning, a patient living in Stamford, Connecticut, phoned to tell me that his son, aged eight or nine, had vomited, had abdominal pain, and a temperature of 103°F. An acute appendix was the most likely diagnosis and I instructed the father to bring the boy to my office at once, adding that I would arrange with Dr. Berg to operate immediately. The father then told me that he was a director of a well known Hospital and that, if I had no objection, he would like to have Dr. X operate. As Dr. X was a surgeon of high standing, I told the father that I saw no reason why he should not do so. Operation disclosed an empyema of the appendix, and when the swollen appendix was being lifted out of the belly, it burst. I saw the pus dripping into the abdomen, giving me a fright I have never forgotten. Fortunately the boy made a good recovery in spite of the mishap.

Dr. Berg performed many hysterectomies for me, which he did with such smoothness and speed, no matter how complicated the operation was, that I would often remark to him, "A. A., you are a mighty good general surgeon, but as a gynecologist you have no peer." He was also a past master at resecting the colon for carcinoma, and among his and my most grateful patients are those



who recovered and who were fortunate enough not to have had a recurrence—a majority of the cases, I am happy to say.

Another example of most skillful work I had the good fortune to observe as recently as last October. A young man, in his twenties, was sent to me complaining of pain in his right lower quadrant, with a temperature of 102°F. I felt a mass in that region, which was extremely tender, and diagnosed it as an acute appendix. As the boy had no means, I sent him into a Hospital ward for operation. The admitting physician elicited a history from him that as a young lad he had had amoebic dysentery, but that he had had no recurrence in recent years. After x-ray examinations and other tests, the conclusion was drawn that the present condition was due to the amoebic dysentery, and the patient was sent back to me with the suggestion that he be given injections of Emetin. When I examined him again that day, I found the mass to be more definite and more tender than before. I took the young man to Dr. Berg who recommended an exploratory operation. On opening the abdomen, he found a mass of adhesions involving the lower end of the ileum, a definitely inflamed appendix and cecum. He resected the lower end of the ileum and a piece of the ascending colon beyond the mass involved. The report from the laboratory on the specimen was "tubercular ulcer of the cecum." The young man made a good recovery and is enjoying excellent health.

My complete confidence in Dr. Berg is evidenced by the fact that he took out the appendices of four of my grandchildren and performed an abdominal operation on another grandson. He also removed my own gangrenous appendix in 1937. At my request he began the operation with local anaesthesia; but when he reached the inflamed peritoneum, the pain was so unbearable that I told him that if he touched it again I would be finished, he smilingly replied that he had expected it, hence an anaesthetist was there, ready to put me under ethylene. I woke up in what seemed to me two minutes, and there was A. A. in his white gown, offering to show me my appendix.

In closing I want to say that after a practice of over half a century I can truly say that no doctor ever had a better friend than I have had in Dr. Berg. I am most grateful for this good fortune.

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## CONSENT FOR OPERATION

JOSEPH TURNER, M.D.

In an Anniversary Volume honoring Dr. A. A. Berg for his unique achievements in surgery, it may not be out of place to comment on the acceptance of surgical treatment by patients and The Mount Sinai Hospital's practice of *not* obtaining written consent routinely for all surgical operations. While the question has various legal aspects on which others can speak with more authoritative knowledge, a number of lawyers have considered some of its legal aspects and their views will be referred to later.

The question comes down to this: would the practice of obtaining written consent for operation be a protection or a risk?

It has long been the practice in The Mount Sinai Hospital to obtain written consent for operation in service cases *only* in the event of 1) minors admitted to the children's surgical wards; 2) patients originally admitted to a medical ward in the expectation that they were to be treated medically, but subsequently found to be in need of a surgical intervention, and therefore transferred to a surgical ward, and 3) patients requiring mutilating operations which would result in permanent loss of body tissue and change of body function, such as enucleation of an eye, amputation, permanent colostomy, sterilization.

In the case of a minor, the consent of the parent or guardian is required under certain laws, and it is desirable to have this consent in a form which cannot be disputed. In the case of adult patients originally admitted to a medical ward, it is thought best to obtain written consent to protect the Hospital in the event that the patient should later claim that admission had been sought only for a nonoperative condition and consent for operation had not been given. But it has *not* been the practice of the Hospital to obtain written consent for operation when an adult patient applies for, and is admitted directly to, a surgical ward in which all of the patients are surgical cases, the ward staff members in charge are surgeons, and the whole function of the ward is plainly surgical.

No consent for operation is sought by the Hospital from any patient admitted as a private patient of a staff member to a private or semiprivate room. No trouble has ever resulted. And so far as is known, no surgeon obtains written consent in his private office from any patient who consults him there.

The practice of obtaining written consent for every operation prevails in many hospitals. The fact is of interest but it is no proof that this is the most satisfactory way to afford protection to the hospital and its staff. Many hospital practices are purely traditional and are followed year after year without review and without clear understanding of the reasons they persist or of the needs they fulfill. A reexamination of the situation as it exists today might pave the way to the adoption of simpler methods, which would still offer modern hospitals a full measure of protection.

As a graduate of the house staff of a hospital where it was routine to obtain written permissions for operation on admission, I know there were occasional

lapses. The consent form gave broad blanket authority to any doctor of the hospital to perform any surgical operation or procedure which in his opinion was indicated. If the paper were literally construed, the patient would seem to be signing away practically every right to redress for injury that might result from an operation. Lawyers say that no individual can legally sign away his real rights and void the protection which the laws give him, and that a written consent in itself does not permit a second party to do injury or commit any unlawful act against the signer.

As regards the basic position of the Hospital, it has assumed that the application of an adult patient for admission for treatment of an illness which requires surgical interference is *prima facie* evidence of his willingness to have an operation performed, and that it is not desirable to complicate matters and perhaps, at times, to delay operation on a patient in urgent need of attention by increasing the formalities incidental to admission. The courts are hardly likely to question the right of a hospital surgeon to operate upon an adult patient who voluntarily seeks admission for surgical treatment.

If one makes it a practice to obtain written consent from these "run of the mill" patients, difficulty will in some instances be encountered because of the patient's physical and mental condition. Thus it may be necessary in emergencies to operate without waiting for written consent, regardless of any rule which may be promulgated. In case of dispute thereafter, the patient then might point to the fact that the general practice of the Hospital was to obtain consent and claim that the absence of written consent in his case was presumptive evidence that consent for operation was not given or intended. On the other hand, if adult surgical patients are regularly admitted without the formality of written consent, the Hospital will always be able, if dispute arises, to point out that the practice of the Hospital is to take consent for granted. It could show that this practice is reasonable and could consistently argue that there is no need to obtain written consent when the circumstances indicate that the purpose of a patient in coming to the Hospital is to seek relief from illness by surgical means.

The patient's intent here is clearly to seek relief from illness; his acceptance of admission to a *surgical ward* indicates his willingness to be treated surgically. To require further evidence of his intent and to ask for a formal written authorization would complicate a very simple matter. If the patient should later claim that he had not given consent to a specific surgical procedure, the blanket authorization might at any rate not be sufficient protection. The Hospital's experiences with other forms of written consent are in point here: the written consent for a necropsy, even though very carefully written, has not itself always been sufficient protection against liability for complaints concerning certain acts on the part of the pathologists.

Is the surgeon sufficiently protected by a written blanket consent to do any operation which he considers necessary without further consultation with the patient? Would it be enough in cases where a surgeon enucleates an eye, amputates a limb, makes a permanent colostomy, or does any surgical procedure which is mutilating and permanent in character? Could not a patient under

such circumstances rightfully claim that he was not informed fully of the character of the operation, that he thought he was signing for something else? Would not the surgeon then still be liable to suit? Would one not have to come back to the question of intent?

While our practice has never been tested in court, tens of thousands of patients have been operated upon without written consent. On very rare occasions, the point was raised that consent had not been *signed*, but no action was ever undertaken after the Hospital's position was made known to inquirers and to their legal advisers.

If a patient should sue and deny having given consent for operation, he would find it difficult to explain convincingly how he came to accept admission to a *surgical ward* where operations are performed daily, without knowing of and consenting to the possibility or indeed probability of operative treatment on himself. Could he have discussed his illness with members of the visiting staff, could he have been taken to the operating room, could he have been given the anesthetic, with no realization of what was going forward, and with complete absence of "consent" on his part? Some patients refuse operation and discharge themselves.

One is referring here, of course, to properly indicated surgical procedures, for a written consent in itself would not protect the surgeon for an operation improperly or negligently performed. Even when written consent has been obtained, the surgeon who operates over the later objection of a patient before operation subjects himself to the risk of a suit.

Moreover, even if the routine prescribes written consents, it is inevitable (human fallibility being what it is) that there will be some cases in which the papers are not properly executed. The omission of the signature can then be considered presumptive evidence of a patient's refusal to give consent. The surgeon who operates, relying upon others to obtain operative consent without checking back himself (this has been known to happen), leaves himself open to a suit.

The Hospital's surgeons have raised the question of written consent for operations several times in the past few decades and the matter has been reviewed each time. It can never be considered entirely closed. The most recent review was made in 1946 by a committee of seven lawyers on the Board of Trustees. The following is extracted from the committee's report:

"The matter was thoroughly discussed. The committee had before it various memoranda on this same question, which had come up periodically. . . . The committee with one dissent came to the conclusion that the Hospital should not get written consents to operations from either private patients or in the wards.

"At the present time the law is clear that the liability for an unauthorized operation is the doctor's liability and not that of the Hospital. This was held in *Schloendorff v. New York Hospital* (Court of Appeals) and is still the law. The case holds that the relation between a hospital and its physician is not that of master and servant. The hospital does not undertake to act through the doctors but merely to procure them to act upon their own responsibility. The



Court further pointed out that there is no distinction between the cases where the operation is performed by visiting or resident physicians. Thus the exemption is present whether the patient be in the private pavilion with his own doctor or in the wards with the services of a staff doctor. The doctor, however, who performs an authorized operation is personally liable.

"Although many other hospitals receive written consent in all operative cases, the practice of our Hospital has been strongly defended by Dr. Turner. He points out that due to human fallibility instances may arise where written consent, if required, might be overlooked by a clerk or such other minor employee entrusted with the procuring of such written consents. Where there has been no course of practice requiring written consent, no inference arises from the failure to obtain the same; but a strong inference might arise in the exceptional case where written consent was overlooked. Furthermore, a broad general consent in writing might be no protection against a claim that the specific operation performed was unauthorized or that the operation went beyond the terms of the consent."

While holding to the foregoing opinion, the committee considered it nevertheless the better part of wisdom to provide against the remote possibility of suit by some ill-advised patient. To cover this eventuality, the Hospital's insurance policies on liability and malpractice now include a clause that protection "shall apply to any claim or suit brought against the insured by reason of an operation performed or alleged to have been performed without the consent of the patient."

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# SURGICAL TREATMENT IN ACUTE HEMORRHAGES OF PEPTIC ULCERS

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As I write this paper in memory of Dr. Berg, I recall the events of the year 1923, when I was invited by the American College of Surgeons to deliver a discourse on local anesthesia in abdominal surgery, as well as on the treatment of peptic ulcers by stomach resection, and when I was also invited to perform operations in various hospitals. Thus I had the opportunity to observe Dr. Berg perform major surgery at The Mount Sinai Hospital in New York and I saw him perform a radical operation for a peptic jejunal ulcer, and greatly admired his excellent surgical technic. When the International College of Surgeons bestowed upon him the great distinction of a "Master of Surgery," he received an honor he justly deserved.

I have chosen as my subject the surgical treatment of acute bleeding ulcers for the reason that I had been invited by Dr. Berg on the 28th of November, 1923, to operate at The Mount Sinai Hospital upon a patient with acute hemorrhage from a peptic ulcer. I was then able to appreciate the definite advantages of a combined local and nitrous oxide anesthesia in a patient who insisted on general anesthesia. The following are the few notes I have on the case.

This was a man aged 51 years, who was rather nervous and gave a history of 2 years of gastric discomfort. He had suffered from considerable colicky pains during the 4 months preceding the operation. Six weeks preoperatively he had sustained a severe hemorrhage with hematemesis and a profuse melena. The bleeding recurred and finally stopped. On x-ray examination a penetrating peptic ulcer of the stomach was demonstrable. Gastric analysis showed a 71/95 *quota* of free and total HCl. Three days preoperatively he suffered repeated hemorrhages. Therefore the operation was decided on and at the patient's insistence it had to be initiated under nitrous oxide anesthesia. I then added local anesthesia of the abdominal wall and the mesentery. The bleeding proved to be caused by a large ulcer near the cardia that had penetrated into the pancreas. I performed a subtotal gastrectomy and left the ulcer *in situ*. Then I did a Hofmeister-Finsterer anastomosis, placed a rubber drain in the abdomen and closed it up. Uneventful recovery and healing occurred.

At a meeting held by the Vienna Medical Society 32 years ago, I suggested immediate operation on any chronic peptic ulcer (proven by the history and by previous examinations) that had its first profuse hemorrhage. This was in contradiction to the general opinion held at the time to treat gastric hemorrhage only by conservative methods. I based my thesis on the fact that out of 18 acutely bleeding peptic ulcers, 15 had been treated to no avail by medical procedures previously. I stressed the fact that hemorrhages without antecedent gastric pains caused by an acute ulcer or by a gastritis should be treated by medical measures. In cases of persistent or recurring hemorrhage exploratory

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Medical Director: Professor Dr. Hans Finsterer.

laparotomy is indicated in order to rule out bleeding, originating in a callous peptic ulcer which in turn would call for surgical hemostasis. I also said that local anesthesia should be used in preference to other types of anesthesia because of the considerable parenchymatous damage caused by the resulting anemia of severe hemorrhage.

I emphasized in numerous publications and conferences the need for *early operation* during the first 24–48 hours. Among others, I gave a lecture before the Medical Society in Chicago in 1923 on the importance of early operation for the success of the surgical procedure. In the ensuing discussion, several authors, Ochsner and Alfred Strauss among them, contended that early operation would not be necessary for the simple reason that blood transfusion would successfully bring any bleeding under control. Due to the fact that we had no blood transfusion at the time in Austria, I lacked the personal experience to decide whether or not repeated transfusions could compare favorably with surgery.

It was said, that surgical treatment of acute hemorrhages due to ulcers and particularly early operation would have a considerably higher mortality than medical measures. A comparison was made in that medical procedures would have a 5 per cent mortality as compared to a 38 per cent surgical mortality. Borsoek, in 1908, figured out this number out of 86 cases published in the literature. This comparison does not prove anything, because completely dissimilar cases were compared with one another. Even in considering only those cases of acute and severe hemorrhages treated medically, and excluding those patients who suffered only minor or occult hemorrhages, the mortality of medical procedures is considerably higher according to Aitken, Bulmer, Chiesmann, Kalk, Umber and others.

Aitken reported on 262 cases of bleeding ulcers who were admitted to the London Hospital between 1929 and 1933. They had an 11 per cent mortality notwithstanding the fact that most patients only suffered minor bleeding. Out of 63 severe hemorrhages, 31 patients were treated exclusively by medical procedures, and 17 of them died. Eleven patients had the benefit of a blood transfusion. Out of this group 3 died. Twenty-one were finally operated on (mostly gastroenterostomies) and 7 died. In 3 patients, postmortem revealed the erosion of a major vessel. Aitken concluded that at least one quarter to one half of all patients with severe hemorrhages die as a result of it.

Bulmer of the Birmingham Hospital reported in 1927, that the mortality of 218 hemorrhages due to acute peptic ulcers was 8.3 per cent, whereas bleedings referable to chronic ulcers had an 11.6 per cent mortality, as demonstrated in 249 cases. The mortality in 89 males comported 16.8 per cent and in 160 females, 8.7 per cent. It is of particular interest to note, that up to 1917, the mortality of acutely bleeding ulcers was between 6 and 10 per cent, that it increased to 15 per cent during the next 10 years in spite of improvements in internal therapy and despite blood transfusions. Bulmer gave an explanation for this when he said that due to the transportation facilities by automobile, many cases were brought to the hospital that formerly died either at home or while under transportation. The second fact, according to Bulmer, is the considerably increased dose of morphine given as compared to that given in former years.

According to Chiesmann between 1925 and 1931, 137 males and 54 females were admitted to the St. Thomas Hospital for bleeding peptic ulcers. The mortality of the males was 27 per cent and of the females 15.6 per cent. The total mortality of the 191 patients was 25 per cent. Those patients who had a hemorrhage lasting over 24 hours, or recurrences at short intervals, had a 74 per cent mortality, as 46 died out of 62 such patients; thirty-eight out of 48 males and 8 females out of 14. The postmortem examinations revealed 45 cases with a major eroded vessel in the base of a callous and penetrating ulcer.

Kalk of Berlin reported in 1936 that 99 patients who were admitted to his medical service with bleeding gastric ulcers had a 12 per cent mortality within the preceding 10 years. Twenty-four bleeding duodenal ulcers had a mortality of 16.7 per cent. Umber (Berlin) had 41 fatalities out of 433 bleeding cases due to ulcers, 280 of which had severe hemorrhages.

If results of surgical versus medical procedures are compared, only those patients should be considered who had the benefit of an early operation without any previous medical treatment within the first 24 to 48 hours after the onset of the bleeding. I published a paper on early operation for bleeding ulcers in 1943 and stated that this early operation was carried out only on rare occasions. In reviewing the available literature I was only able to find 76 early operations with 6 fatalities, a 7.8 per cent mortality. By that time, I myself had performed 114 early operations with 7 fatalities, a 6.1 per cent mortality. This was good proof of the fact, that the old view expressed over 40 years ago, that medical procedures would be superior to surgery in cases of acute and severe hemorrhages of peptic ulcers, does not hold true today.

Gordon-Taylor's publication on the comparative results of medical and surgical procedures of acutely bleeding ulcers at the Middlesex Hospital is of particular interest. Gordon-Taylor had only 2 fatalities out of 22 early operations between 1919 and 1924, indicating a 9 per cent mortality. Within the next 2 years the mortality rose to 40 per cent, mainly because of a higher number of late operations (10 operations with 4 fatalities). As a result of it, the acute hemorrhages were again treated by medical procedure between the years 1924 and 1933. There was a total mortality of 24 per cent, and in those who had recurrent bleeding, it even reached 76 per cent. Under the influence of these disheartening results, as achieved with medical procedures, Gordon-Taylor resumed his original attitude toward early operation. He was thus able to save patients whom other surgeons had declined to operate upon previously.

It had been repeatedly asserted, that blood transfusions would render early operation unnecessary, as it would not only substitute the amount of blood lost, but also increase the blood clotting, by favoring the production of blood platelets. It was also said, not to give large transfusions (1000 cc and more) lest the thrombosis formation at the site of bleeding be washed off by the rising blood pressure. There is a general agreement on the value of blood transfusions as a preoperative measure. The hemostatic component, however, can only be effective in flat and bleeding ulcers or in an erosive gastritis, where the bleeding is caused by a decreased clotting tendency. There are some internists, who overestimate the hemostatic effect of blood transfusions, and who consequently use them in any



kind of bleeding, including profuse hemorrhages due to eroded arteries. Umber, on the other hand, has used transfusion only rarely (in 433 acute hemorrhages he gave only 38 transfusions) because severe hemorrhages in which a hemoglobin of 20 to 25 per cent of normal prevailed were also cured on his service without transfusion. Aakersberg, at a meeting of the Nordic Surgical Society in 1940 pointed out the fact, that blood transfusion proved worthless in 65 instances out of 72 patients with severe peptic hemorrhages. In 5 cases he saw a possible—and in 2 cases a probable beneficial result in that it had some kind of hemostatic effect. He went so far as to declare the hemostyptic effect of blood transfusion a myth. Westermann denied any hemostatic effect of blood transfusion, and Jennings even contended that it had a detrimental effect, fatal in at least 25 per cent of those patients. As a result, blood transfusion was discontinued completely at the Cumberland Hospital, and no further fatalities were observed in this group of patients.

The differing evaluation of the hemostatic effect of blood transfusions depends on the type of the acute bleeding. A hemorrhage due to a shallow peptic ulcer or due to a gastritis is sure to be controlled by blood transfusion, as this type of bleeding is possibly also caused by a delayed clotting ability of the blood. Also, in cases of bleeding from minor mucosal vessels at the margin of a callous ulcer hemostasis will be achieved, with or without transfusion. A major artery squirting at the bottom of a penetrating ulcer such as the pancreatico-duodenal artery may, have formed a thrombus owing to the fall in blood pressure in the course of the circulatory collapse accompanying the bleeding. A major blood transfusion of a 1000 cc, or even more, with the resulting increase in blood pressure is instrumental in displacing the thrombus and, consequently, the hemorrhage will start afresh with renewed vigor. This may partly account for Jennings' failures. If such patients have recurrent bleeding 2 or 3 days after the transfusion, this is likely to be due to the hyperacid gastric content, which is not diluted by food intake, than to the transfusion. The hydrochloric acid will then decompose the thrombus formation as no food is ingested to bind the acid. Jennings saw no further fatalities on his service after having dispensed with blood transfusions. Two facts account for this. He was fortunate not to have a major squirting vessel among his cases after that, and he operated on his patients before the hemorrhage had a chance to recur. According to my own viewpoint, the complete disrepute of blood transfusion as being noxious, is not justified. As a method of blood substitution and as a preparatory measure for a late operation, blood transfusion is still indispensable.

Many internists contend that bleeding due to erosion and the ensuing death are a very rare occurrence. No matter how often they reiterate this statement, this was flatly contradicted by my own experiences at operation and particularly in the late operations. A publication by Seidl is also to this effect. Bruns, (of Gottenbrück) reports, that in Jagie's Clinic within a period of  $6\frac{1}{2}$  years only 2 out of 53 patients with hemorrhages had to be operated on, and that the remaining 51 patients were successfully treated for their bleeding peptic ulcers by medical procedures and were all cured. Kalk (1936) pointed out that he saw

fewer fatalities at Bergmann's Clinic in Berlin for a period of 13 years, than on the medical service of the Westend Krankenhaus in Berlin within only 2 years. This is explained by the fact, that the University Clinic admits only selected cases, whereas the medical services of the County Hospital have to admit all emergencies. In Jagie's clinic there was no fatality due to hemorrhage in the course of  $6\frac{1}{2}$  years. At the Lainzer Krankenhaus, however, where all emergencies including acutely bleeding peptic ulcers from the Vienna area have to be admitted twice weekly, 24 fatalities due to acutely bleeding ulcers were recorded within a single year, according to Seidl. At postmortem, a major vessel was found eroded at the base of a penetrating ulcer. Therefore one must rely on the experiences of a hospital ward, if one is to evaluate fatalities due to bleeding peptic ulcers and not the numbers of deaths encountered in a University Clinic.

There is another argument against the need of a surgical approach to bleeding peptic ulcers and particularly against early operation. The ulcer is said to be not the sole cause for the hemorrhage, furthermore that the clinical diagnosis would therefore be unreliable, and that even during the operation, the source of bleeding can not be located in all instances. I want to refer to two publications by Blumer (Birmingham) and by Hansen (Sweden) in order to show that peptic ulcer is the most frequent source of bleeding. Blumer was able to find peptic ulcers in 467 cases, 48.89 per cent of all hemorrhages whereas only 25 cases were due to cirrhosis of the liver (with 8 fatalities), 7 cases were due to carcinoma and 1 case to portal thrombosis and 2 cases were melena neonatorum. Twenty-four cases with 3 fatalities were due to so-called parenchymatous bleeding occurring in gastritis. Based on postmortem findings, Hansen was able to find in 393 fatalities due to hemorrhage; a bleeding peptic ulcer in 202 cases, 51.4 per cent; 91 fatalities, 23.2 per cent due to cirrhosis of the liver; 51 cases 13 per cent, due to carcinoma, whereas in 49 cases, 12.4 per cent, other causes for the hemorrhage were found.

In view of the fact, that chronic peptic ulcer represents the most frequently encountered source of an acute hemorrhage, one has to think of a bleeding ulcer in the first place in making a diagnosis. This will be confirmed by the history of the patient and by former findings. The uncertain cases are the exception to this rule. It would therefore be most beneficial for the patient, if those on whom a chronic peptic ulcer was established to be the source of bleeding, to be subjected to an early operation. If a cirrhosis of the liver becomes a problem in the differential diagnosis as to the source of bleeding, there still is the possibility of a concomitant bleeding ulcer. In those cases in which there is a doubt as to whether an ulcer is present or not, it is good practice to wait. Should the hemorrhage occur, however, surgery must be performed in order to rule out a peptic ulcer.

Thirty years ago I had to operate on a 60 year old tavern keeper because of an acute gastric hemorrhage. Previously he had but slight pain due to hyperacidity when he suddenly vomited large quantities of dark blood postprandially. I thought of a cirrhosis of the liver in the first place, as this man was a chronic alcoholic. The bleeding recurred at a short interval and his attending physician, who had but recently lost 2 patients because of

acute gastric hemorrhages urged me to operate on him, which I did 12 hours after the onset of the first bleeding. It was an exploratory laparotomy, done on March 28th, 1920. I found a cirrhosis of the liver with considerably distended veins on the gastric surface, and I also found a peptic ulcer located in the cardiac third of the stomach, callous in appearance and extending into the lesser omentum. I performed a curved resection with a Hofmeister-Finsterer anastomosis. The specimen showed a large eroded vein. The patient healed and felt perfectly well for the next 6 years, when he died of a cerebral vascular accident.

Without the benefit of surgery, this patient would certainly have bled to death from this eroded vein, just as he would have died of a ruptured esophageal varix. The exploratory laparotomy was a life saving procedure, as I was able to demonstrate the ulcer immediately after opening the peritoneal cavity.

In cases of apparent cirrhosis of the liver on exploratory laparotomy, where the stomach and the duodenum seem to be outwardly normal, gastrotomy should additionally be performed in order to palpate the two structures with the ungloved finger in order to rule out peptic ulcer before being satisfied with a diagnosis of an esophageal varix. We had two failures on my own service; in one patient gastrotomy was omitted, in the other one the surgeon palpated with the gloved finger.

On May 21, 1938, a 51 year old woman was admitted to my service because of severe gastric hemorrhage. She had had a slight gastric discomfort over a period of 3 years and had sustained a severe hemorrhage 6 months previously. She also had a history of heartburn for the past 5 months. On admission, a definitely enlarged liver and ascites were found. The bleeding occurred in the afternoon and recurred at night. I decided to do an exploratory laparotomy on the following morning after a blood transfusion. I found a markedly cirrhotic liver but no peptic ulcer. I did not perform gastrotomy for digital palpation of the stomach and the duodenum from within, but considered the probability of a bleeding esophageal varix and closed the abdomen. Twelve hours later the woman died. The postmortem revealed a cirrhosis of the liver and an enlarged chronically inflamed spleen. There also were hemorrhagic erosions in the cardiac part of the stomach and a duodenal ulcer which had extended into the pancreas, showing a large eroded vessel in its depth. There were 500 cc. of dark coagulated blood in the stomach and the entire intestinal tract was also filled with blood.

The second case was that of a 68 year old locksmith (who was an alcoholic) and who had a 3 year history of heartburn and slight epigastric pain. For 3 days he had tarry stools. Upon admission on July 13th, 1944, he was still bleeding and quite anemic. The attending surgical assistant suspected an acutely bleeding peptic ulcer and operated on the patient immediately. The outward appearance of the stomach was normal and on gastrotomy no ulcer was found. The gastrointestinal tract was filled with blood, and there was a marked cirrhosis of the liver with incipient shrinkage of the liver and ascites. The diagnosis was bleeding esophageal varix. The abdomen was closed. The patient continued to bleed and died 3 days later. Autopsy revealed 3 flat ulcers, 10 to 12 mm in diameter, in the vicinity of the cardia, as well as the cirrhosis of the liver. In one of the ulcers, a branch of the gastric artery was eroded. Small and large bowel were both filled with blood.

In the first case, it would have been easy to palpate the ulcer on gastrotomy and, thereafter, to perform a gastrectomy which undoubtedly would have been life saving. In the second case, the flat ulcers were not detected with the gloved finger. Here also, this patient could have been saved by a curved resection. I have repeatedly stressed the performance of gastrotomy and digital palpation with

the ungloved finger in those cases in which the ulcer is not demonstrable externally. This enables the surgeon to palpate even flat duodenal or gastric ulcers.

Six patients were admitted to my service who had a severe hemorrhage due to ruptured esophageal varices and cirrhosis of the liver; they all died as a result of it. Three cases were diagnosed correctly clinically and no operation was performed. Three of these patients were operated on, because they also complained of gastric pain, but there was no ulcer demonstrable and they only had cirrhosis of the liver. All 6 had shown at postmortem examination cirrhosis of the liver and bleeding esophageal varices.

A rare cause of acute gastric hemorrhage, which can hardly be diagnosed clinically, is an ascending invagination of the jejunum after gastrectomy with anterior gastroenterostomy and an enteroanastomosis.

A 26 year old actor had a gastrectomy performed with an anterior gastroenterostomy and an enteroanastomosis in May 1938, in Munich. He felt well until the end of June 1945, when he had occasional colicky pains. On the 20th of August 1945 he was admitted to my service because of a gastric hemorrhage. During the preceding night the patient had developed hematemesis two hours after an unusually severe and "crampy" spell. This bleeding had recurred. A gastrointestinal series done 5 months previously had revealed a small gastric stump following a Billroth II resection with precipitate emptying of the stump. Calcium gluconate and *Sangostop*, as a hemostatic agent were given at first on the assumption that this hemorrhage was due to gastritis. Exploratory laparotomy was decided upon, to be carried out on the following morning, as the hematemesis had been apparent during the night. A gastric stump of good size was found at the operation, as well as an anterior gastroenterostomy and an enteroanastomosis. The gastric stump as well as the anastomotic loop was filled with blood. Ten cm. distal to the enteroanastomosis, the neck of an ascending jejunal intussusception was seen in the efferent loop, and this mass which had a sausage-like appearance had extended into the afferent loop through the enteroanastomosis. Reduction was impossible because of the beginning necrosis of the invaginated gut. The entire anastomotic loop along with the invagination was therefore resected as well as a strip of the gastric stump two finger breadths. An end to end anastomosis of jejunum was done and distally an end to side anastomosis. The fixation of the mesocolon was technically difficult. After insertion of a rubber drain, the abdomen was closed. Healing by primary intention occurred, but the patient developed a right sided parotitis which resolved after surgical drainage. According to a written report, this patient is devoid of any pain.

The foregoing case illustrated a very rare cause for a gastric hemorrhage and also disclosed an unusual anatomical finding. In fact, it is the first ascending intussusception of the small intestine that I have seen in 40 years in over 10,000 laparotomies. Obviously no exact clinical diagnosis as to the origin of the bleeding can be made in such a case.

The objective of the early operation within the first 24 to 48 hours which I had suggested 30 years ago is twofold: the operation is to avoid fatal bleeding on the one hand and the perforation of the bleeding ulcer, on the other. The fact that lethal bleeding is not a rare occurrence if the patient is only treated by medical procedures was already discussed. This was also proven by the publications of Chiesmann of the St. Thomas Hospital and by Gordon-Taylor of the Middlesex Hospital, who had a 78 per cent mortality in those cases in which bleeding had recurred. A very instructive case was published by Friedemann who favors early operation in acutely bleeding peptic ulcers.



A 52 year old man who had had gastric pain for a long time and two negative gastrointestinal series, suddenly developed a severe hematemesis due to gastric bleeding (he vomited 1000 cc. of blood). The patient's pulse was not felt on admission. He immediately received 1000 cc. of defibrinated blood with *Calorose* as well as 20 cc. of a 10 per cent solution of sodium chloride intravenously. Nine hours later a second severe hemorrhage occurred and another 1000 cc. of blood were vomited. He received a blood transfusion. Twenty-four hours later he sustained another hemorrhage and received a third transfusion after which he apparently did well. A nocturnal hematemesis ensued on the third morning (750 cc. of blood). He received an injection of *Clauden* (hemostatic) and a gastric lavage with a 2 per cent silver nitrate solution was performed. One hundred cc. of activated *vivocoll* were also instilled by a stomach tube. On the same evening he received another 1000 cc. of whole blood. On the fourth day he had another severe hemorrhage and a thready pulse. On that evening another hematemesis of 750 cc. occurred. He received 1 teaspoonful of NaCl by mouth. On the fifth day there was considerable melena and the patient's condition declined rapidly terminating in death. The autopsy revealed a duodenal ulcer, the size of a nickel, that had extended into the pancreas and that had eroded the pancreatic duodenal artery.

In this case, it certainly would have been more beneficial to explore the abdomen after the onset of the bleeding or after the second hemorrhage, despite the two negative gastrointestinal series. The penetrating ulcer would have been found and an early radical gastrectomy could have been performed.

The other objective of an early operation is to prevent the bleeding ulcer from perforating. An acute perforation of a bleeding ulcer, though not very common, does still occur in some instances. The statement of Behrend that acute bleeding and perforation never occur conjointly, because the perforated ulcer usually is chronic and would have a fibrous base, whereas a prerequisite for a gastric hemorrhage would be the hemorrhagic tissue of an acutely fresh gastric ulcer, is both wrong in theory and practice. The important role which perforation actually plays in an acute bleeding ulcer is shown by Bennet's postmortem findings who saw 61 hemorrhages from peptic ulcers with concomitant perforation in 25 cases. Some authors, Aitken, Bulmer, and Thiele in figuring out the mortality rate in medical treatment for ulcers, omit those fatalities which are due to perforation. This seems to me to be unjustified, as timely surgical intervention in a bleeding ulcer can prevent its perforation. Prognosis of such a complication is undoubtedly grave but some patients of this group will be saved by a timely operative procedure. Gordon-Taylor was able to save 4 out of 5 such patients who had simultaneously hemorrhage and rupture of the ulcer, by a gastrectomy, whereas the fifth patient (perforation of a bleeding peptic jejunal ulcer) died postoperatively. Kunz was only able to save 3 out of 9 cases by surgical intervention. On my service, 10 patients were admitted who had hemorrhage and perforation. Six survived operation. One of these cases is of particular interest because a recurrent and fulminating hemorrhage occurred in the 4th postoperative week for bleeding and ruptured ulcer, due to an erosion of the pancreaticoduodenal artery.

A 56 year old man, who had postscarlatinal valvular heart disease and who also had stomach complaints for the past 3 years was admitted to the 4th medical service on January 29th, 1943, because of gastric pains. Four days after admission, while under medical

treatment, a severe hematemesis occurred and recurred during the night. On the following morning he had severe pains. Six hours later the patient was transferred to the surgical service with the symptoms of a peritonitis due to a ruptured viscus. There was considerable anemia (1 million erythrocytes; Sahli, 30 per cent of normal), the pulse was barely palpable and the rate was 138. There was a board-like abdominal wall and no dullness over the liver. Operation was performed immediately under local anesthesia and 25 cc. of ether. The peritoneal cavity was suctioned with the Aubert aspirator. The small and large bowel were found also filled with blood. The stomach was considerably dilated and contained blood and ingested food. Aubert suction was applied. There was a callous ulcer of the anterior duodenal wall with a perforation about the size of a pencil in diameter, which was stopped by a food particle. The rupture was covered with stitches; a draining tube was inserted, and the abdominal wall closed. In this case a so-called Witzel fistula was performed at the cecum according to the suggestion of Pauchet, because of the super-imposed peritonitis. A blood transfusion was immediately started, and the bowels were irrigated through the Witzel fistula and rectally with sodium sulfate in order to remove its toxic blood contents as quickly as possible. Healing by primary intention occurred and, on the 22nd of February, the patient was re-transferred to the 4th medical service for further postoperative care. On the 25th, in the evening, there occurred another severe hemorrhage with circulatory collapse. During the night he received a blood transfusion but was found moribund on the next morning. The red blood cells showed 1.1 million erythrocytes and a Sahli of 20 per cent of normal. The pulse rate was 140 and only palpable over the carotid artery. Despite his poor general condition, I had the patient transferred to my service. During laparotomy, 1000 cc. of *Tutofusion* were given intravenously as a donor was not immediately available. His radial pulse was felt again after that. Mid-size laparotomy was done under local anesthesia using one quarter per cent novocaine solution. There were only a few adhesions and the stomach was found to be empty, whereas the small and large bowel were filled with blood. The ulcer in the anterior duodenal wall was found to be covered with stitches. There was another ulcer on the posterior duodenal wall, which had extended into the pancreas. At its bottom the pancreatico-duodenal artery was found to be eroded and temporarily closed by a loose thrombus. The artery was closed by stitches, and the duodenum as well as half of the stomach resected. I closed the duodenum and made a Hofmeister-Finsterer anastomosis, inserted a rubber drain, and closed the abdominal wall. The patient was given a blood transfusion and *Homoseran*. The bowel was irrigated through the still cecal fistula. Uneventful recovery occurred. Three weeks later the patient was re-transferred to the 4th medical service to be treated for the severe anemia. He improved slowly, gaining 22 lbs of weight since his discharge from the hospital and feeling well since, now, 7 years after this last operation.

The cure of this seriously ill patient was only possible through immediate operation following his hemorrhage and rupture. Furthermore, only a quarter per cent of novocaine solution was used because of his severe anemia and, despite the superimposed peritonitis, the blood was drained through the cecal fistula which would otherwise have acted toxically, if absorbed. The application of a cecal fistula, as suggested by Pauchet is not indicated in acute hemorrhage if no perforation occurs. This is rendered unnecessary because those patients who had the benefit of local anesthesia will have an almost immediate resumption of their peristalsis after bowel irrigation and will therefore evacuate the blood in the bowels within 24 hours.

At the French Surgical Congress in 1933, it was erroneously stated in a report by Papin and Wilmouth on acute hemorrhage caused by peptic ulcers, that I would operate on any gastric hemorrhage, irrespective of its cause. Also Schonbauer discussing a report by Felsenreich, stated that a bleeding ulcer would be

an absolute surgical indication for me. This dictum has also been erroneously interpreted, as I have stated as long ago as 1918, in my first conference on the operative treatment of gastric hemorrhage and reiterated ever since in every publication, that I assume an expectant attitude in cases of acute hemorrhage due to a fresh peptic ulcer without preceding history of gastric discomfort. I order a blood transfusion, if deemed necessary, and only choose to operate if the bleeding recurs. Then I perform an exploratory laparotomy in order to rule out a silent chronic peptic ulcer which I then remove surgically.

Of 257 patients with acute hemorrhage, who were admitted from August 1st 1936 up to the end of 1946, to the surgical service of the Allgemeines Krankenhaus, 58 were not operated on. In 3 cases bleeding due to cirrhosis of the liver was clinically suspected and proved by autopsy. Forty-four patients had a hemorrhage due to a silent acute peptic ulcer, which did not recur, however. Those patients were either transferred to a medical ward or discharged after a week's observation. One case was probably due to a hemorrhage from a flat peptic jejunal ulcer which responded to medical treatment. Ten patients had a hemorrhage due to a chronic ulcer, 7 of which subsided within the first 24 hours despite severe initial symptoms (syncopes). The gastrectomy for their ulcers was therefore postponed until the bleeding-free interval. Three patients were transferred to my service for a belated operation after fruitless treatment on a medical ward although they were moribund. Two of them died while blood transfusion was being administered and the 3rd one at the beginning of the laparotomy. All three cases at postmortem proved to be penetrating ulcers with a large eroded artery. These three patients could have probably been saved by timely operation.

The results obtained by surgery do not only depend on the technic and on the type of procedure but, above all, on the degree and on the duration of the anemia with its concomitant visceral and cardiac degeneration. Therefore the results of early operation are found to be better than those achieved after delayed operation. In the first years, mostly palliative surgery was done which controlled the bleeding without attempting to cure the ulcer. The following graphic chart details the comparative results achieved (table I.)

Gastroenterostomy, which was almost exclusively performed 50 years ago, if operation was decided on at all, is at best instrumental in controlling the bleeding only in flat ulcers with conjoint spastic pyloric contraction, because it enables the stomach to empty and contract adequately. For this reason Tixier and Clavel lately declared it to be fully satisfactory. In callous and penetrating ulcers this method is of no avail, as this type of stomach will not contract and no hemostasis will result. I have only performed gastroenterostomy during my first years as assistant at Hochenegg's Clinic because resection for peptic ulcer was forbidden even in the absence of gastric hemorrhage. I had 1 fatality out of 7 early operations. At autopsy, the eroded arteries were found at the base of a gastric ulcer but had extended into the pancreas.

In cases of duodenal ulcer that penetrate into the pancreas and which are not safely resectable because of the localization and extent, in instances of concomitant hemorrhage I do an exclusion of the pylorus instead of the resection for exclusion. Technic: The pylorus is excluded by ligature of the antrum with

encircling stitches proximal to the pylorus, and a posterior gastroenterostomy is done. Then I put a large tampon on top of the duodenum which bulges the abdomen wall. A firm laparotomy dressing applied at the end of the operation thus presses the duodenum against the ulcer base and controls the bleeding. I have seen this type of hemostasis to be absolutely reliable at the autopsy of one case of belated operation who had blood filled small intestines when operation was performed, and an empty small intestine at the time of autopsy on the patient who died 10 hours after operation. This dressing, however, must be loosened after 24 hours in order to avoid injury to the pancreas. In cases with ulcers of the lesser curvature, the gastric coronary arteries were closed with stitches in

TABLE I

*Acute and profuse hemorrhages due to peptic ulcers operated on from January 1, 1912-December 31, 1948*

	EARLY OPERATIONS		LATE OPERATIONS	
	Num-ber	Fatalities	Num-ber	Fatalities
Gastroenterostomy .....	7	1 = 14.2%	7	3 = 42.8%
Gastroenterostomy with ligature of the an- trum .....	3	—	14	4 = 28.5%
Closure with stitches of coronary gastric arteries according to Witzel .....	4	—	—	—
Excision of the Ulcer .....	6	1 = 16.6%	7	4 = 57%
Typical $\frac{3}{4}$ gastrectomy including the ulcer 1917-1948				
I. Private hospitals .....	86	2 = 2.3%	64 (58)	15 = 23.4% 9 = 15.5%
II. Surgical Service of the Allg. Kranken- haus .....	88	4 = 4.5%	75	16 = 21.3%
Total .....	194	8 = 4.1%	167 (161)	42 = 25.1% 36 = 22.3%

4 cases, according to the Witzel procedure, and in 6 cases excision of the bleeding ulcer was performed with 1 fatality.

The most currently used procedure is the two thirds gastrectomy with the Hofmeister-Finsterer anastomosis. This technic yielded good results in the early operation group. Out of 174 gastrectomies we had 6 fatalities (i.e., 3.4 per cent mortality). In private hospitals I only had 2 fatalities out of 86 gastrectomies (2.3 per cent mortality).

An 80 year old man had had a peptic ulcer of the stomach for 40 years, resulting in stenosis and considerable loss of weight due to emesis (he weighed 34 kgs. and was of normal stature). I planned to perform a gastroenterostomy but, on the night preceding the scheduled operation he sustained a severe circulatory collapse. The following morning his pulse rate was 130 and barely palpable. The upper abdomen was bulging due to the stomach being filled with fluid, which on lavage proved to be blood. Immediate operation under local anesthesia was done (May 29th 1927). The mesentery was anesthetized with one quarter per cent novocaine solution. The stomach extended into the true pelvis and was filled



completely with blood. Four liters (quarts) of bloody fluid were aspirated. There was a large callous ulcer on the lesser curvature which extended up to the pancreas. Another ulcer was found at the pylorus. The half gastrectomy and duodenal resection were easily performed. A Hofmeister-Finsterer anastomosis was done. Postoperatively the pulse rate was 136, on the 2nd day, 100, and on the 3rd postoperative day, 80. There was uneventful recovery and the patient was out of bed on the 5th day. On the 8th day the patient developed a bilateral pneumonia and died 2 days later. There was no postmortem.

A 43 year old man had gastric discomfort for the past 6 years. Three months previously he had sustained a severe hemorrhage and 3 days before the operation he developed a high temperature (la grippe); one day before operation he had a severe fainting spell and ejected large quantities of bright red blood, and there also was melena. During the night his bloody vomitus had recurred. When he was brought to the hospital the next morning, his pulse rate was 126 and barely palpable and there was considerable anemia (3 million erythrocytes and a 35 per cent hemoglobin). He was operated upon (July 10th, 1933) under local and splanchnic anesthesia with one quarter per cent novocaine solution. A duodenal ulcer which penetrated into the pancreas was found. There was also an ulcer in the anterior duodenal wall which was just on the point of rupturing. Small and large bowel were filled with blood. An erosion of the pancreatoduodenal artery was found at the base of the ulcer upon resection and bleeding was acute. The artery was closed with stitches and a typical gastrectomy was performed. There was an uneventful postoperative course. The pulse returned to normal on the 3rd postoperative day, but there still was a severe and febrile bronchitis. First a left sided and then a bilateral pneumonia developed, and the patient died 17 days later. There was no postmortem.

On my surgical service results achieved with gastrectomy which I myself carried out in most cases, are not as good (88 resections with 4 fatalities i.e., 4.5 per cent mortality). Even here the mortality is not any higher than in gastrectomy for non-bleeding peptic ulcers. In the 4 fatalities, 2 were due to pneumonia and 2 to peritonitis.

Early operations were carried out in patients with really severe and sometimes most severe hemorrhages. This is proved by the fact that the bleeding was accompanied in most cases by dizziness or by frank syncope. In 30 cases, the main branch of the pancreatoduodenal artery was found to be eroded at the base of a penetrating ulcer or, in other cases, the main branch of the left gastric artery, or, in one case, the splenic artery, and in 2 cases the mid-colic artery was eroded in a bleeding peptic jejunal ulcer.

In the delayed operations, results are not encouraging, neither on my surgical service nor in those patients who were operated on at the Garnisonspital No. 2 during World War I or in those operated on in various private hospitals.

Out of 21 patients who 30 years ago had mere gastroenterostomy done or exclusion of the pylorus by ligature of the antrum, 7 died because of their already considerable anemia. Out of 7 cases who only had the bleeding ulcer excised, 4 have died as the sequel of their anemia.

In the typical two thirds gastrectomy, there were 31 fatalities out of 139 patients (22.3 per cent mortality). It is correct to state that in 6 of these cases there was no connection either with the acute bleeding or with the operation.

A 49 year old officer (operated on April 30th, 1918 at the Garnisonspital No. 2) died 3 weeks later of a recurrent dysentery. At autopsy the resection line was completely healed but the colon showed extensive damage due to the dysentery.

A 50 year old man (operated on March 25th, 1921) died of diabetic coma (no insulin treat-

ment was available at the time), 3 weeks postoperatively after an uneventful postoperative course.

A 72 year old man (operated on August 31st, 1929) had an extensive icterus for the last 6 weeks and recurrent gastric hemorrhages of 4 days duration. At operation a gastric ulcer which had extended into the pancreas was apparent. Besides the common duct was compressed by a pancreatic tumor. Gastrectomy and cholecystostomy were performed. The patient died 2 weeks later because of uremia.

A 44 year old man (operated on January 30th, 1930) had a hemorrhage of 4 days duration due to a peptic jejunal ulcer which had developed 20 years after a gastrectomy. Five days after the radical operation, he had to be reoperated on, because of a perityphlitic abscess, which was surgically drained. The patient died one week later with septicemia. Two patients had a hemorrhage for 6 and 10 days respectively and their ulcer had ruptured and blood filled the peritoneal cavity causing death 7 and 11 days respectively later, due to progressive peritonitis.

Even deducting those 6 fatalities, which were not caused either by hemorrhage or by the operation, mortality still runs as high as 18.7 per cent. The main single factor causing death was the parenchymatous degeneration due to the prolonged anemia. The latter could not be reversed by the hemostatic and substituting effect of blood transfusion.

Eight patients died merely of their severe anemia, whereas 6 others had developed pneumonia which was due to adverse external circumstances, as up to 1938, the patients had to be wheeled to and from the operating table through a court yard, winter and summer. Four patients died of peritonitis, 2 of whom had hematogenous peritonitis originating from a tonsillitis which was in turn caused by hemolytic streptococci. Two patients died of syphilitic aortitis, a 69 year old man died 12 days postoperatively with a pulmonary embolism, a 57 year old woman died 6 weeks postoperatively. She had healing by primary intention but suffered from considerable anemia which necessitated her transfer to the 1st medical service 2 weeks after operation. At postmortem the gastric status revealed no pathologic findings, but she was found to have a pyopneumothorax which went undetected and untreated.

The results of late operation are not satisfactory, but are still very much better than those results which this group of patients would have met with, if further medical treatment only would have been continued. The mortality of medical procedures is very high in those patients whose hemorrhage continues more than 24 hours or recurs within the next few days. Chiesmann's very important statistics to this effect quote a 74 per cent mortality (46 fatalities out of 62 cases). Gordon-Taylor had a 78 per cent mortality at the Middlesex Hospital in this group of patients. At Denk's Clinic 10 patients of 23 died, as they had medical treatment only, despite recurrent hemorrhage. In spite of the poor results of late operation, I have never turned down a single case, if such a patient was sent to surgery as a last recourse, because of previous fruitless medical treatment and of imminent fatal bleeding. The following case of a very old and desperately ill patient demonstrates that even in the old age group in a seemingly hopeless situation, results may be achieved.

An 85 year old general on whom I had performed a posterior gastroenterostomy because of a peptic ulcer of the stomach 30 years previously, when I had been an assistant at Hochenegg's Clinic, had been treated on various occasions for gastric discomfort and had

recovered from a severe gastric hemorrhage in 1938, and had been subject to more frequent abdominal pain lately, for which he had received fruitless medical treatment. Two weeks preoperatively this patient sustained a severe hemorrhage due to a peptic ulcer of the jejunum which recurred 3 times despite all available medical treatment including several blood transfusions. He had a severe anemia (2 million erythrocytes and a Sahli of 30 per cent). Because of his pain and the progressive weakness, the patient insisted strongly on operation. His attending physicians were all opposed to surgery in view of his old age. I myself was in favor of the operation when consulted in the case. It was carried out on March 11th, 1943, with a preceding blood transfusion. Local anesthesia for the abdominal wall was used, and one quarter novocaine solution for the mesentery. There was a large peptic jejunal ulcer which had penetrated the mesocolon and transverse colon and was just about to rupture into the colon. Half of the stomach was resected together with the anastomotic loop and the ulcer base remained *in situ*. I did an end to end anastomosis according to Hofmeister-Finsterer. I inserted a rubber drain and closed the abdomen. The patient received a postoperative blood transfusion and one on the following day. Uneventful postoperative course and healing by primary intention. There was also a severe bronchitis and he had considerable trouble with his prostatic hypertrophy causing him to need a permanent catheter. Despite all this the patient was discharged 3 weeks after the operation.

A distinction must be made between patients with acute and profuse hemorrhages and those who are subject to secondary anemia as a result of repeated and minor hemorrhages. Mikulicz has professed an absolute surgical indication for this latter group more than 50 years ago. These patients had a considerable anemia (1 to 1½ million red cells, hemoglobin, 20 to 45 per cent of normal). Up to 30 years ago these patients were exclusively subjected to a gastroenterostomy, which had been declared to be the method of choice by Krönlein in 1906. Thirty-five years ago, when I was assistant at Hoehenegg's Clinic, I also performed a gastroenterostomy and I had 1 fatality out of 6 such operations, due to the erosion of the splenic artery on the 6th postoperative day. Ever since 1918, I performed typical resection in patients with secondary anemia due to peptic ulcer, with the exception of those patients treated by resection for exclusion. Up to 1942, I had 4 fatalities out of 65 resections (6.1 per cent mortality).

A 36 year old man died of a pulmonary embolism; a 62 year old woman died of her severe anemia 3 days after the operation in spite of repeated blood transfusions. A 70 year old woman died 19 days postoperatively because of anemia and of acute endocarditis associated with bilateral pleurisy. A 36 year old man died of an acute pancreatitis.

The results of resection in cases with secondary anemia are satisfactory if one considers the fact that 17 patients were between 60 and 76 years of age. Only 2 of this group died. Lately the cases of severe secondary anemia due to minor and repeated hemorrhages are less common because these patients are operated upon earlier.

Gordon-Taylor who is a fullhearted supporter of early operation concluded his address delivered before the Mid-Staffordshire Medical Society on October 8th, and published in the Lancet, 1935, with this sentence: "Finsterer's first forty-eight hours is still the optimum period for surgical attack in hematemesis and the golden age of gastric surgery will have been attained only when all cases of hemorrhage from chronic ulcer come to operation within that space of time.

Let there be no procrastination, for delay is fraught with peril; early enterprise is the prelude to success."

It will be quite some time before the general practitioner and above all the internist will have been convinced of the great importance of early operation in profusely bleeding peptic ulcers and thus refer their patients for early operation. Until we will have reached this goal, we as surgeons, have the moral obligation, irrespective of statistics, to operate on those patients who are sent to us for late operation after unsuccessful medical treatment has been given to them. Even then we are still able to save more lives than with continued exclusive medical treatment.

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# THE ROMANCE OF THE MODERN ERA OF BLOOD TRANSFUSION

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The transfusion of blood as a safe, harmless and reliable procedure represents a recent accomplishment of which the medical profession can be indeed proud. It is deemed "recent" because until 50 years ago, transfusions of blood were haphazard procedures and represented spectacular performances which satisfied the vanity of the doctor more than they helped the patient.

To recount the development of blood transfusion during the last few centuries is a big undertaking and only a few brief remarks on its history are contemplated here.

It was natural that transfusion of blood could not be planned until Harvey discovered the circulation of the blood in 1616, and only 50 years later, in the year 1666 was the first attempt made to transfer blood from one animal to another. Lower (24) performed many careful experiments on dogs, using a silver cannula not unlike those used in the early part of this century for artery-to-vein anastomosis. His treatise makes interesting reading. In order to prevent overloading of the circulation, he bled the recipient dog before starting the transfusion. To him belongs the credit for the first exsanguination transfusion, not in the manner in which we know it today, as an attempt to cure disease, but simply as a resuscitation experiment; the transfer of blood from another dog followed immediately upon the bleeding of the recipient dog.

In the following year Lower and King (25) reported from England a blood transfusion from a sheep to a patient. They first performed some blood letting on the patient and then injected 7 ounces of sheep's blood with good effect. In the same year Denis (10) in France performed blood transfusions on 2 patients. For the next 150 years blood transfusions consisted solely in the transfer of animal blood to patients.

A great step forward was taken in the early part of the last century when Blundell (3, 4) performed a number of transfusions using, for the first time, blood from a human donor. He had shown in a series of carefully planned animal experiments that transfusion of blood from one species to another was fatal; that, for instance, transfusion of blood from a sheep or a human to a dog was followed by death either immediately or after a brief period. On the basis of these experiments he insisted on using humans only in human blood transfusion, and he was the first to discontinue the use of animal blood in transfusions to humans.

Coagulation of the blood posed a serious problem in blood transfusion. As physicians did not have a safe way of preventing blood coagulation during its transfer from donor to patient, the use of defibrinated blood continued to be the method of choice, until Carrel (7) and Crile (9) in the early part of this century, introduced vessel anastomosis. It should be stated that as early as 1852, Schiltz (30) warned against the use of defibrinated blood. However, up to the introduction of the citrate method no simple technique was available for blood transfusion as vessel-anastomosis, syringes and paraffinized glass cylinders were cumbersome.

How quickly times and techniques change! Until 20 years ago all these methods would have required a detailed description, as each had strong supporters, each clinic favoring one or another apparatus. All these methods became only of historic interest, as the citrate method came into universal use. It has always been most surprising to me that the problem of overcoming the coagulation of the blood during transfusion was not solved long before 1915.

Many of the more modern techniques for uniting the vessels of donor and recipient which were in use during the early part of this century were employed centuries ago. For instance, Lower and King (1667) not only used cannulae, but a piece of an artery taken from the neck of a horse or an ox in order to bridge the gap between 2 cannulae which they had inserted into the blood vessels of donor (lamb) and recipient. The 3-way stop cock was described and employed by Blundell. A number of early illustrations show metal and glass syringes and rubber bulbs for propelling the blood.

In 1868 Belina (2) published a very careful compilation of all the transfusions reported in the literature between 1820 and 1868. He collected 155 cases during these 48 years, an average of about 3 cases per year. Defibrinated blood was the method of choice. Eighty-three cases were transfused for metrorrhagia by many different operators. In those days profuse bleeding from the uterus presented the chief indication for transfusion. Up to 24 ounces of defibrinated blood were transfused for a large variety of other diseases. Sixty-six among these 155 cases died following the transfusion. Many of these deaths seem to have been due to hemolysis or infection. This is not surprising, if we remember that Belina's report antedated the Lister era as well as Landsteiner's work on blood groups. Among the serious sequelae of transfusion were vomiting, chills and convulsions, i.e. typical hemolytic reactions.

Landsteiner (19) published his epochal work on human blood groups in 1901. Like many great discoveries, it was presented in a brief communication. Today it seems hard to believe that Landsteiner's observations on the 3 blood groups (a fourth group was added in the following year by Descatello (11)) were not used immediately in human blood transfusion and that 10 years elapsed before Ottenberg (27) applied Landsteiner's work in practice. This long delay was partly explained by the fact that in the early part of this century transfusions were used rarely, possibly because in those days the difficult transfusion technique stood in the way of their popularity. Another factor was that Landsteiner's work was published in Austria where blood transfusions were not used. If his paper on the blood groups had been published in this country where great interest had been shown in blood transfusions since Carrel's and Crile's work, the course of events might have been different.

Forty years later, Landsteiner (in cooperation with Wiener (20)) added another important milestone to our knowledge of the blood groups by the description of the Rh factor. The last word in this chapter has not yet been spoken. It is most likely that further work by his pupils (Landsteiner died 8 years ago) or others will further clarify some thus far unexplored fields.

Blood grouping was undoubtedly the most important single advance in the

modern era of blood transfusion. However, transfusion would still have been a rarely used therapeutic measure if, at about the same time, the citrate method had not taken the place of other complicated methods. With syringes, paraffinized glass cylinders or similar instruments the present popularity of blood transfusion would have been impossible.

Anti-coagulants seemed to offer the best and only prospect for the solution of this problem. Naturally others had had the same trend of thought. For instance, Braxton-Hicks (5) who used sodium phosphate and Wright (31), using sodium oxalate, had tried unsuccessfully to use anti-coagulants. Hirudin, glucose and bicarbonate of soda had also been employed without success. The best known anti-coagulant was, unquestionably, sodium citrate. This drug had been used for many years in laboratory work at a strength of 1 per cent in order to keep blood fluid for blood chemistry or blood cultures. It seems incredible that until the end of 1914 nobody studied this chemical carefully as to its toxicity and effect on the clotting time of the recipient's blood.

The successful solution of this problem was effected by a carefully planned group of animal experiments, which I performed in the laboratory of Mount Sinai Hospital in cooperation with Dr. George Baehr. Thus, when I performed my first citrate transfusion on a patient on January 7, 1915, it did not represent a "shot in the dark." The preliminary work on dogs made the human citrate transfusion a safe procedure.

The experiments were planned to give answers to the following questions:

1. What is the minimum dose of sodium citrate which will prevent coagulation of the blood?

2. What is the toxic dose? Would the minimum dose, necessary to prevent clotting during blood transfusion, be within the range of safety?

3. Will sodium citrate lengthen the clotting time of the recipient's blood, thus making the transfusion of citrated blood inadvisable and dangerous?

1. Minimum dose: To 10 test tubes containing 0.1 cc., 0.2 cc., etc. up to 1 cc. of a 10 per cent sodium citrate solution, 10 cc. of blood taken from a narcotized dog were added and one test tube containing 10 cc. of blood was kept as a control. The 0.1 per cent citrated blood clotted just as quickly as the control. The next tube (containing 0.2 per cent citrated blood) did not clot for 2 days and then began to present a soft blood clot. The next tube (0.3 per cent) showed identical findings. The test tubes containing the higher percentages of citrated blood were still fluid after 3 days. These experiments were repeated a number of times with identical results. When human blood was tested, the results were the same. Thus it was established that a 0.2 per cent mixture of sodium citrate with blood will prevent coagulation for at least 2 days and that 1 per cent is an excessive and unnecessarily high dosage.

2. Maximum non-toxic dose: If citrated blood be the universal method of transfusion it should be applicable in large transfusions (up to 1500 cc.). If citrated blood in view of the hazard of toxicity should be used only for small transfusions (up to 200 or 250 cc.) its usefulness would be limited. Three hundred cc. was removed from the carotid artery of an anesthetized dog mixed with



0.06 gm. of sodium citrate and reinjected into the jugular vein of the same dog without any untoward symptoms (observation time, 2 weeks). These experiments were repeated a few times with identical results. In order to establish the toxic dose, 15 cc. of a 10 per cent solution of sodium citrate were injected intravenously into a dog weighing 11 lbs. The animal died almost immediately. This experiment was twice repeated with identical results. Thus 15 gm. of sodium citrate would be fatal to a patient weighing 110 lbs. As a transfusion of 1500 cc. of citrated blood does not require more than 3 gm. of sodium citrate, large citrate transfusions are perfectly safe, even in a debilitated patient.

3. The third set of experiments was planned to answer the most important question: What happens to the coagulation time of the patient when citrated blood is injected? Three hundred cc. of blood were taken from an anesthetized dog, mixed with sodium citrate at the rate of 0.2 per cent and immediately reinjected. Tests taken a few minutes after the injection showed shortening rather than lengthening of the coagulation time. Similar results were obtained in our third patient who received a citrate transfusion (January 11, 1915). After a transient acceleration of the coagulation time, it returned to normal, thus making citrate transfusion applicable for general clinical use before, during, and after operation, as well as in hemorrhagic diseases and in all other indicated conditions.

My first publication on this subject appeared in January, 1915, (21) reporting not only the results of careful animal experiments, but 2 successful human blood transfusions, in which the patients received 300 cc. and 500 cc. of citrated blood, respectively. In the same month, Agote (1) reported a successful citrate transfusion. Agote's publication did not mention any previous experimental work. Evidently no study of the coagulation time in the recipient or of the maximal non-toxic dose of sodium citrate had been made. His dosage (0.25 per cent) was practically identical with mine.

It should be pointed out that Hustin (16) had done previous work on citrate-glucose transfusion which he had presented before the Brussels Medical Society in April, 1914, and which was published a few months later. That neither Agote nor I knew anything about Hustin's work is readily explained by the fact that the first World War began in August 1914, and communication between this hemisphere and the European continent had ceased. However, as I pointed out in a second paper (July, 1915) (22), even if we had known of his paper before we began our work, neither Agote nor I would have interrupted our investigations, for Hustin did not solve the problem. He made the error of assuming that, in order to prevent coagulation, he had to mix citrated blood with equal parts of glucose solution. He gave one transfusion of 150 cc. of blood mixed with sodium citrate and 150 cc. of glucose solution. Such a strong dilution of blood could never have come into practical use. For instance, if we wish to give a patient 500 cc. or even 1000 cc. of blood, it would be impractical to add 500 or 1000 cc. of glucose solution; it would dangerously overload the patient's circulation and deprive him of the benefit of undiluted blood.

Hédon (14) investigated the same problem, the use of sodium citrate in blood transfusion, in 1917 unaware of the work already done in 1914 and 1915. After

he published the results of his experimental work, in which he reached the same conclusions as in my paper of 1915, he received letters from Hustin, Agote and myself. Hédon (15) fully acknowledged the priority claims of Agote and myself, but said with reference to Hustin's work: "Hustin combined equal parts of blood with isotonic glucose-salt solution, containing a certain proportion of sodium citrate and injected this mixture in small quantities. Hustin's method is really an infusion of strongly diluted blood mixed with citrate of soda and glucose."

In the latest book on blood transfusion by a group of British clinicians and pathologists, published in 1949, Keynes, in presenting the history of blood trans-



FIG. 1. Complete outfit for transfusion of Citrated Blood. Author's technique 1915. Originally 50 cc. of a 2 per cent solution of sodium citrate were used for 450 cc. of blood. In later years 5 cc. of a 30 per cent solution were mixed with 500 cc. of blood. The glass dropper was added about 1925.

fusion, expressed the same opinion as Hédon. "Hustin's work came to nothing because he assumed that it was necessary to mix the citrated blood with equal parts of glucose solution so that the blood was greatly diluted. Agote and Lewishohn arrived, however, at the same conclusion at almost the same moment, establishing that 0.2 per cent sodium citrate acts as an efficient anticoagulant without toxic effects, unless the total amount of citrate exceeds 5 gm."

The apparatus which I suggested for the citrate transfusion in 1915 was very simple. It consisted of a graduated glass beaker for the collection of the blood and its citration, and a salvarsan flask as it was used in those days for intravenous salvarsan therapy (figs. 1, 2 and 3). While others tried to introduce

complicated procedures for the citrate transfusion, I continued to employ a simple method. The latter from the very beginning insured the complete separation of the donor and the recipient which ultimately permitted the transport of the donor's blood from blood banks over distances of thousands of miles to the recipient (World War II). In order to insure rapid and proper mixture of the blood with the sodium citrate solution a large cannula must be introduced into the donor's vein.

The often repeated claim that sodium citrate when mixed with blood caused chills in some unexplained manner was disproven by Rosenthal (23). He showed that immediate thorough cleansing and autoclaving of all instruments employed



FIG. 2. Taking blood from the donor. A rubber tube leading from the cannula to the bottom of the glass jar is not shown in this picture. The use of sterile gowns and sterile gloves for doctors and nurses is essential in order to insure complete asepsis.

in a transfusion (cannulae, rubber tubing, etc.) and the use of triple distilled water effected a reduction in the percentage of chills from 12 to 1 per cent. At present double distilled water is used. An even more impressive figure was published by Satunov (Novgorod) quoted by Filatov (13), namely, a drop from 53 to 2 per cent, after he had introduced the Mount Sinai Hospital technique of cleansing the instruments and preparing the solutions.

It is interesting to point out that the figure of 1 per cent of chills occurring among 477 transfusions, quoted in the previous paragraph, was arrived at in 1932 (from October 1, 1931 to October 1, 1932), when the open method was used at The Mount Sinai Hospital and employed ever since 1915. Even after the introduction of the blood bank in 1938, the open method continued to be used for many years both for the collection and injection of the citrated blood with excellent results.

The citrate method was originally planned for blood transfusions to be carried out intramurally in two stages (taking the blood from the donor and injecting it into the recipient) and to be executed within a comparatively short time interval of about 1 to 2 hours. I am convinced that this original technique is preferable to the storage of blood and its transportation over wide areas, because the vital

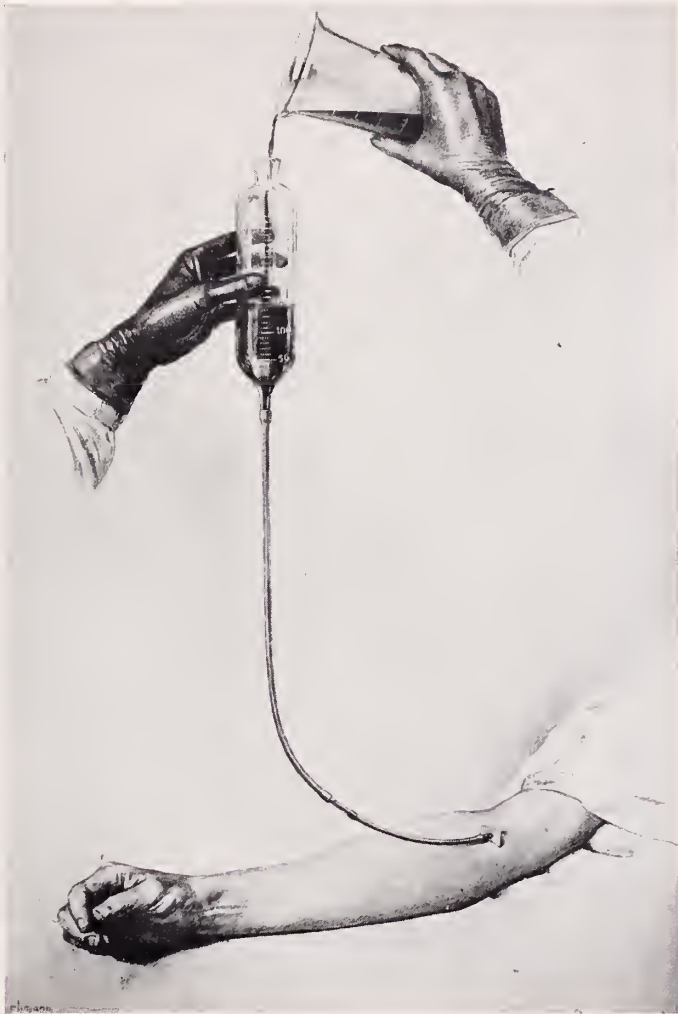


FIG. 3. Infusion of citrated blood into the recipient.

cellular blood elements are more apt to maintain their molecular structure unchanged, if their extravascular life is of short duration.

However, it was natural that the ease with which citrated blood could be transported would soon speed the transport of blood over wide areas. Brem (1917) (6) was the first to carry citrated blood from donor to recipient over a distance of 70 miles by plane. However, these early attempts remained abortive. No extensive use was made of them in World War I, whereas blood transport was



widely used during World War II. During the invasion of the Continent 1000 pints of citrated blood were flown daily across the Atlantic to the battle front. Group O blood was used exclusively, thus making it immediately available for wounded soldiers without further tests. This airlift would have been impossible without previous citration of the blood.

The normal life span of the erythrocytes in circulation averages 100 to 120 days. However, their life span may be shortened, when blood is extravascularly stored. Attempts to lengthen the life of the red cells have been moderately successful; at least half a dozen different preservatives have been suggested. The disadvantage in all these solutions is the fact that they materially dilute the blood, whereas in an immediate transfusion from donor to recipient as little as 5 cc. of a 30 per cent citrate solution may be used for 500 cc. of blood.

The first paper on the preservation of red blood cells *in vitro* was published by Rous and Turner (29) in 1916. They used a mixture of sodium citrate and dextrose. At the time of publication it appeared to be merely an interesting laboratory study dealing with the survival of the blood elements, outside of the circulatory system. However, when blood banks were introduced 20 years later, their original work became of great importance and laid the foundation for the development of similar preserving media.

The first to make use of Rous' work, though on a small scale, was Robertson (28) during World War I. When a battle was expected, he collected blood, mixed it with sodium citrate and dextrose and kept it ready for immediate use, when the wounded were brought in from the front to the first aid station.

With the introduction of the Blood Bank by Yudin (1936) (32) and Fantus (1937) (12) stored blood has gradually replaced immediate transfusion from donor to recipient. Blood banks have undoubtedly come to stay, though they have some inherent disadvantages, among them an increase in post-transfusion reactions. However, the advantages of easy procurement in times of emergency, of immediate availability of any blood group or subgroup, and the financial economy of a properly conducted bank have made them very popular. The blood bank would probably not have achieved its present popularity and universal use in large medical centers, if World War II had not made imperative the procurement of huge quantities of citrated blood for shipment overseas.

When stored blood is a few days old, there is frequently encountered some clot formation. For this reason, it is advisable to cover the flask with gauze in order to prevent these coagula from reaching the circulation of the recipient. Formerly, when the donor's blood was reinjected within a short interval, such precautions were unnecessary as no clot-formation occurred.

For stored blood the vacoliter bottle which contains sodium citrate, dextrose and citric acid as a preservative is widely used. For immediate transfusion from donor to recipient the old method (open glass beaker and flask), which I have suggested in 1915, is still the best. The objection that such an open method might carry infection to the recipient by contamination from the air is purely theoretical. Experience over a period of more than 30 years has shown that such objections have no basis in fact. The open method is just as safe as any closed method, if complete asepsis is insured.

Adherents of the closed method point to the danger of air-borne infections when open methods are employed. If air-borne infection played any role in our operative procedures we should return to the pre-aseptic era and use Lister's carbolic acid spray. Infections in a sterile field are due to faulty technique in the operating room (personnel, sterilization of instruments, etc.) not to air-borne

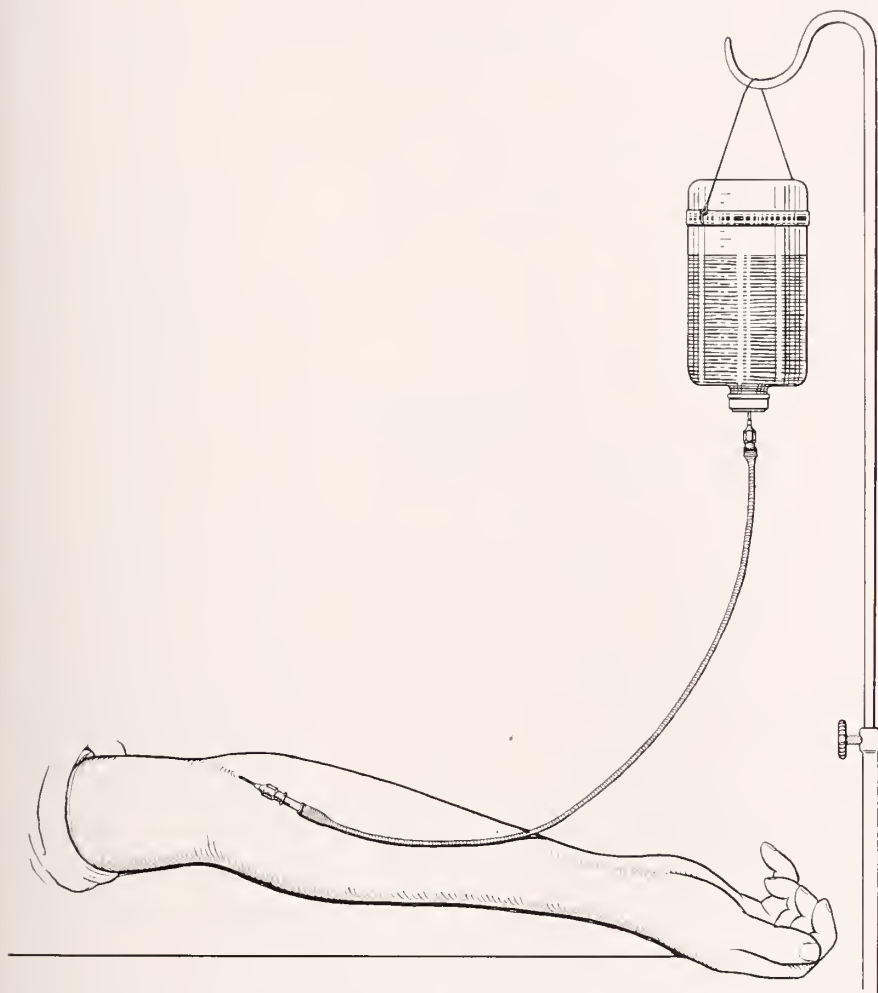


FIG. 4. Vacoliter technique (closed method). Taking the blood from the donor.

infection. If such infections play any role, we could not, for instance expose large portions of the brain for several hours, without having patients succumb to meningitis. In fact, we could not perform any procedures without strong anti-septic support.

I have no quarrel with anyone who, for any reason (e.g. lack of proper facilities for autoclaving) prefers to use the closed method. For instance, in transfusions in the doctor's office or in private homes, when fresh or recently stored blood is

used and before the blood is allowed to sediment any considerable length of time, the closed method, in the form of vacoliter bottles, may be used to advantage (figs. 4 and 5). Furthermore the closed method is the ideal method for use behind the battle front.

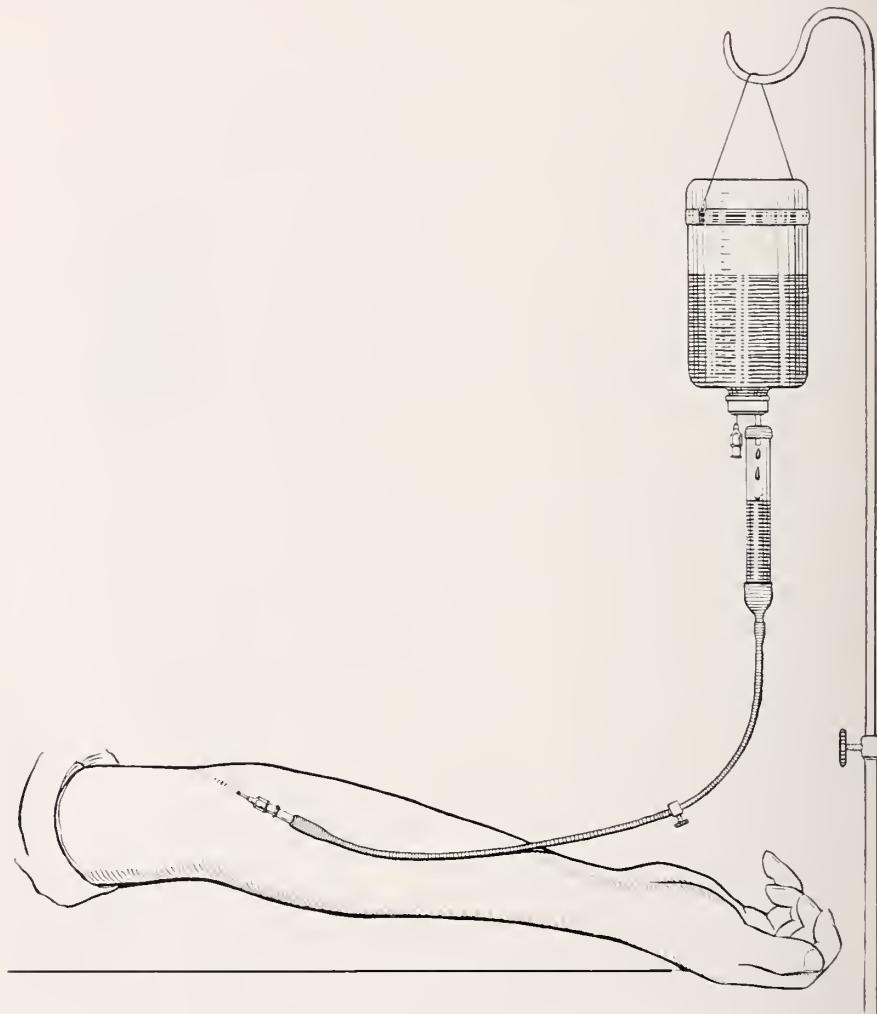


FIG. 5. Vacoliter technique (closed method). Injection of blood into the recipient.

The closed method however, is not ideal for routine transfusions in a hospital where bank blood collected a number of days before, is used. In employing a closed system for the infusion, the free flow of blood is apt to be impeded by coagula. It is much safer to combine the closed and the open methods and, after removing the cap from the vacoliter bottle, to filter the stored blood through gauze (thus removing the clots), as shown in Fig. 6, before injecting it into the patient (figs. 7 and 8).

It is only fair to point out that from the standpoint of economy the closed method may be preferable. In a large institution like Mount Sinai Hospital where thousands of transfusions are given yearly the closed method may represent considerable saving. With the open method a large nursing staff is required to cleanse and autoclave all glassware and rubber tubing after every transfusion. With the closed method this work is done by commercial houses. After their use, glassware and rubber (or plastic) tubing are returned to the factory in exchange for sterile sets. A very reasonable amount is charged for such service.

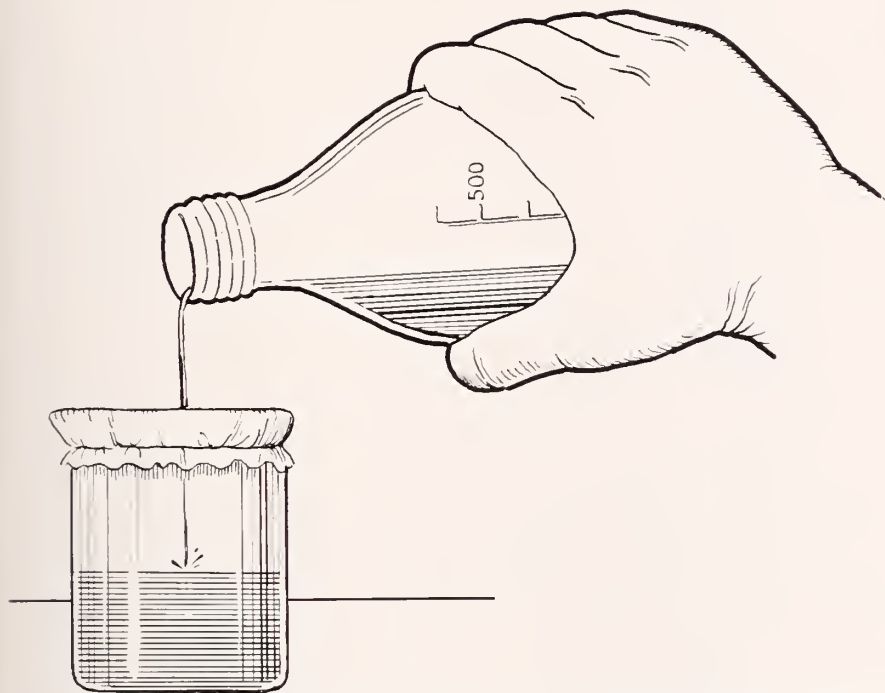


FIG. 6. Blood is poured from the Vacoliter Bottle into a glass beaker, covered with gauze, thus separating the fluid blood from its coagula. (Combined closed and open method.)

It is not surprising that postoperative reactions (high temperature and chills) are observed more frequently since the universal use of stored blood. As stated above, citration of the blood was used originally in order to keep the blood fluid for 1 or 2 hours. The experiments which I reported showed conclusively that this technique is not meant for long storage, for instance, 5 or 6 days. Even mixture with Rous' solution or similar preservatives, will probably not prevent early changes in the red blood cells, leucocytes or platelets, not recognized by laboratory tests. As I have pointed out, the advantages of a blood bank in a large community and in large hospitals are so evident that we have to overlook some of the disadvantages.

In recent years a serious post-transfusion complication, homologous serum



jaundice, has been observed in a sufficient number of cases to warrant a brief discussion, although no exact figures of its occurrence are available. At one time infectious hepatitis appeared to follow blood transfusion in about 0.5 per cent

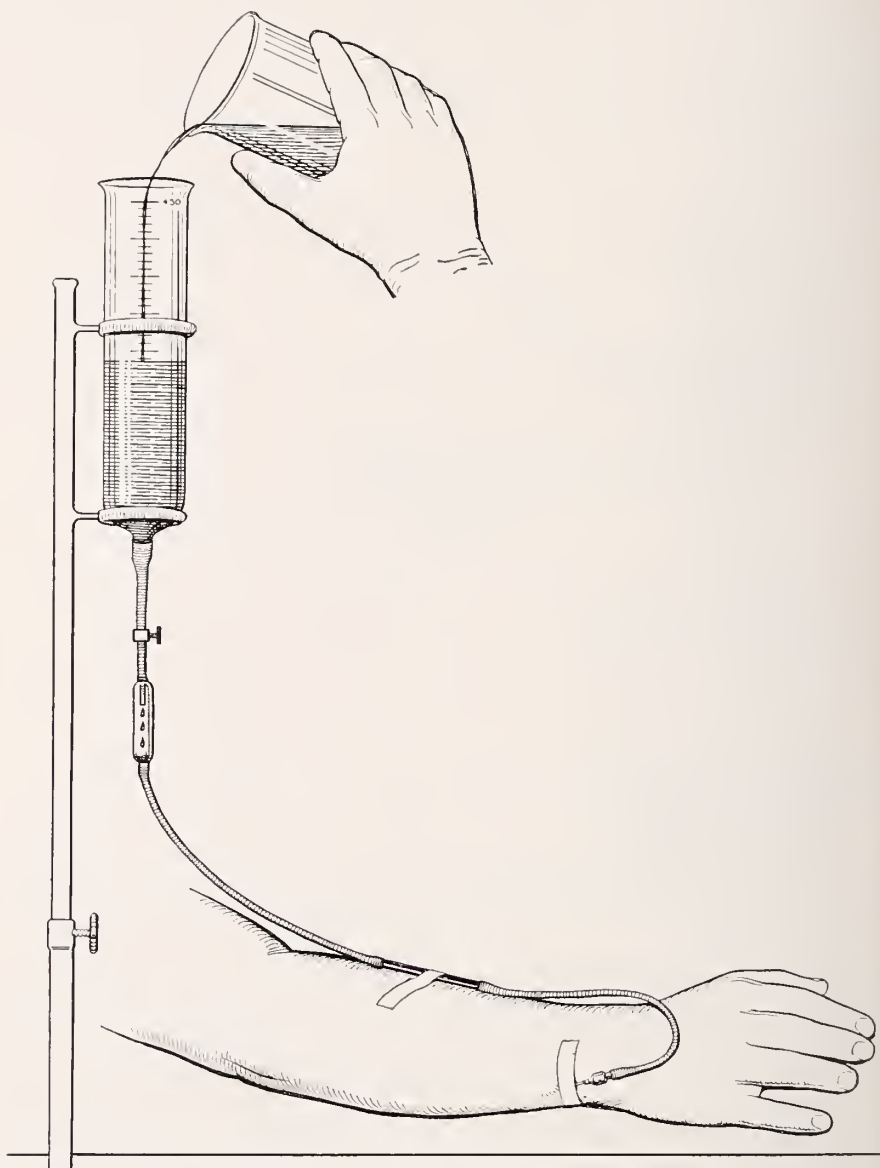


FIG. 7. The blood is poured into the flask.

of transfusions and in 3 per cent of the pooled plasma in one institution. The fact that a number of patients suffering from this complication have died, requires the combined efforts of clinician and virologist to safeguard the patient against post-transfusion hepatitis.

The real etiology of this form of hepatitis is not definitely established. It is assumed to be due to a virus which is transmitted from the donor. The fact that the donor may be apparently free of symptoms before or at the time his blood is taken makes avoidance of the transfer of this virus disease with its serious complications uncertain. The recipient often fails to show any symptoms until about 2-3 months after the transfusion, when icterus and an enlarged liver

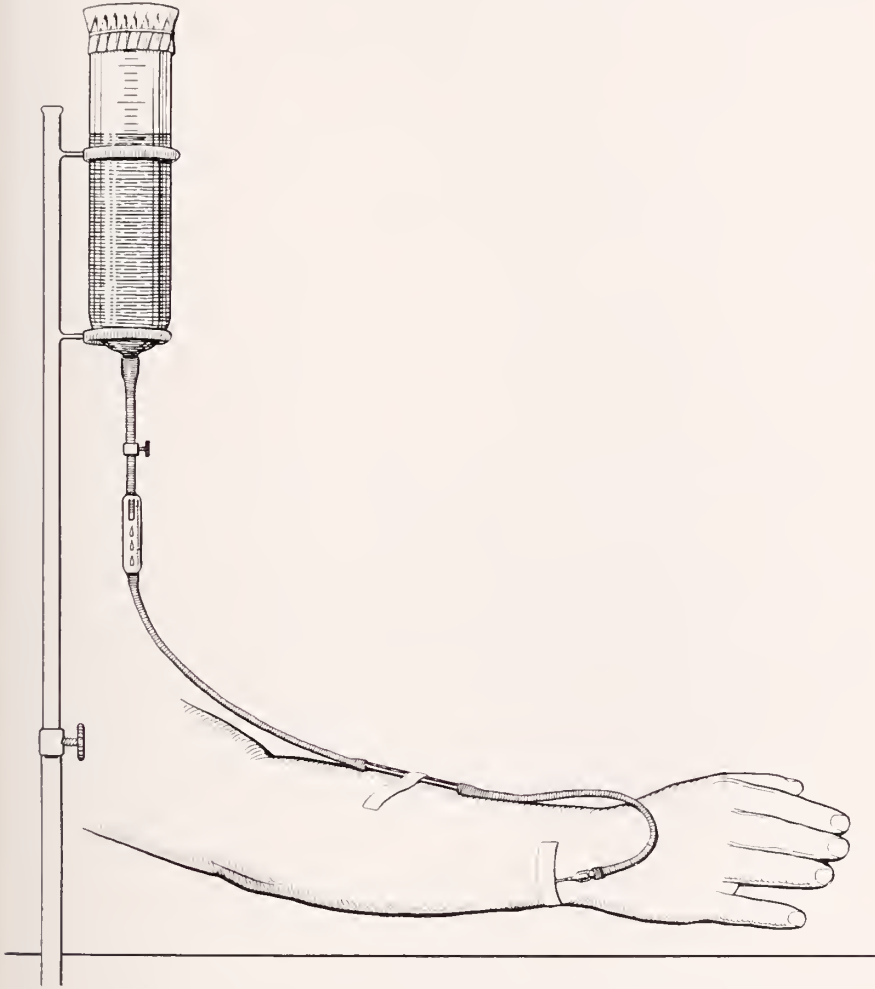


FIG. 8. The blood is slowly entering the circulation of the patient.

appear. Sometimes no manifest symptoms are present in the donor to indicate underlying hepatitis.

The modern antibiotics have no curative effect in post-transfusion hepatitis. Most cases subside after a few weeks or months. Nevertheless, unless we find some means to safeguard the patient against this complication, blood transfusion will become discredited. Some non-toxic drug or other method must be found which will kill the virus in the donor's blood. In other words, every unit of blood

taken from the donor should not only be citrated, but mixed with this preventative. Nitrogen mustard has been tried, but it is not a harmless drug, even when given in small quantities. Plasma has been irradiated with some benefit. However, our present methods of irradiation do not appear to be effective in whole blood. In view of the grave danger of a homologous serum jaundice following plasma transfusion, the use of plasma should be reduced to a minimum.

The rapid rate at which the number of transfusions has increased in recent years is most striking. At the Mount Sinai Hospital, 143 transfusions were given in 1923 (bed capacity 669 beds), 477 in 1932 (728 beds), 794 in 1935 (785 beds), and 2097 in 1941. In recent years the records have been kept by the blood bank. These records do not show the number of transfusions, but the units distributed by the blood bank to the different parts of the hospital; 5269 units were distributed by the blood bank in 1948, each unit consisting of 500 cc. of citrated blood. In 1949 the number of units rose to 9546.

There seems to be a tendency in recent years to give very large transfusions. For instance, a transfusion of 5000 cc. of blood during or immediately following a major operation is by no means the exception. It is possible that infusions of such very large quantities of blood may occasion grave after-effects. Of course, it is important to check the haematokrit during the transfusion in order to guard against overloading the circulation.

The rapid rise in the number of transfusions after the introduction in 1938 of the blood bank is most impressive. Undoubtedly with the ease of procurement and the simple technique, some unnecessary transfusions are given. Yet it is remarkable to walk through the operating floor and see transfusions being given simultaneously to 4 or 5 patients in different rooms and for a variety of diseases. The picture of operability and post-operative recovery has changed completely since the wide use of transfusions. Operations which previously seemed hazardous can now be undertaken with an excellent chance for a smooth post-operative course. Where formerly transfusions during operation were given only in cases of severe hemorrhage and shock, they are now used extensively as a preventive measure against shock and other post-operative complications.

In the early days of the last war citrated plasma was used extensively at or near the battle fields in the European and Pacific areas. Plasma has the great advantage in not requiring blood grouping. Therefore, in times of great stress it may have had its place. However, blood is preferable to plasma. Only a few plasma transfusions were given at Mount Sinai Hospital during 1949.

Ever since the introduction of sodium citrate as an anticoagulant in blood transfusion in 1915 I have wondered whether some other even better chemical might not be found. Heparin (26) is impractical, as it lengthens the coagulation time of the recipient's blood.

We cannot here discuss the recent interesting and stimulating work of Cohn and his associates (8) on blood fractions. However, sufficient time has not yet elapsed, to properly evaluate their application in all their ramifications.

Thus we have briefly sketched the development of the technical problems of blood transfusion from vague and bizarre attempts to a safe, effective, and re-

liable method. The popularity of blood transfusion is demonstrated by the fact that an index of the world literature on transfusions between 1900 and 1933 published by Koenig and Hesse (18) comprises 4423 articles.

Today transfusion of blood is one of the most important therapeutic agents. It is fair to say that with the exception of the modern antibiotics, transfusion of blood is used in a greater variety of diseases than is any other therapeutic measure. Such progress would have been impossible without the discovery of the blood groups and the introduction of the citrate method of blood transfusion.

#### SUMMARY

A brief review of the history of blood transfusion is presented.

Animal experiments which led to the first successful use of an anticoagulant (sodium citrate) in blood transfusion are discussed.

Post-transfusion reactions have increased since the introduction of blood banks.

During the last few years post-transfusion hepatitis has been observed in a small percentage of the cases.

In order to avoid post-transfusion complications the greatest care should be taken in cleansing and autoclaving all instruments (needles, glassware, tubing, etc.) used for blood transfusion and in maintaining perfect asepsis during the transfusion.

In view of the grave danger of a homologous serum jaundice following plasma transfusion, the use of plasma should be reduced to a minimum.

Indiscriminate use of blood transfusion should be discouraged.

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# VAGOTOMY IN THE TREATMENT OF PEPTIC ULCER NEAR THE CARDIA AND OF PEPTIC ULCER OF JEJUNUM (MARGINAL ULCER, STOMAL-ULCER)

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Having been aware of the role of vagotomy in the treatment of gastralgic crises for some time (Exner, 1928), I resumed this method after Dragstedt's publications. Thus from September 1947 till March 1950 in my department at the Franz-Joseph Hospital, 250 patients suffering from gastric, duodenal or peptic ulcer of the jejunum (marginal ulcer, stomal-ulcer) have been treated by vagotomy. Vagus section also has been performed as an analgesic operation in a few cases of inoperable cancer of the stomach. This new indication was reported on for the first time in the Wiener Klinische Wochenschrift in 1940. Meantime this indication has been recognized by other authors (Grimson and associates, 1950). Of these 250 cases, including all those with indications mentioned, 3 died following operation (meningitis, massive pulmonary embolism, cardiac death). About one year ago the indications for and the method of operation here changed. My opinion is that in gastric ulcer, gastric resection continues to be the method of choice and only in cases when this is impossible without undue operative risk, vagotomy is indicated. In duodenal ulcer, after combining gastroenterostomy and vagotomy, I saw a fair postoperative course and in my opinion the final result of the operation may be improved by combining both methods. The explanation of this fact was given by Dragstedt in 1949 and 1950.

Recently, as a matter of clinical trial, gastric resection was added to vagotomy in a series of cases. The end results will be recounted subsequently. Meanwhile the value of vagotomy is wavering up and down in the literature. The alluring part of vagus section—provided its permanent efficacy—is its low mortality. When ascertaining the average mortality of the reports of 8 investigators cited by Beal (1950), I find in 604 cases, 6 deaths, i.e., a mortality of 1 per cent. Trimble with his associates reports that in the statistics of the American Gastroenterological Society, the mortality in over 2500 cases, both with the transthoracic and transabdominal approach, is 1.7 per cent.

An additional fact is especially noteworthy, it is that these 2500 cases include 61 per cent of peptic ulcers of the jejunum. Again, for reasons not entirely clear the mortality of vagotomy according to a report of Walters and collaborators is 6 per cent in 84 cases and thus the *a priori* opposition of these authors to this new operation is intelligible. According to Trimble and his associates, the mortality of gastric resection for ulcer disease in the reports of various authors is from 1 to 20 per cent. In some series it may even be below 1 per cent. Thus, Walters and his associates, in 1947, of 317 gastric resections had a mortality of only 0.9 per cent, while at the same time in 55 cases of gastroenterostomy there was a mortality of 3.6 per cent. These statistics serve as evidence for the special importance of the selection of cases for each operation. Finsterer's statistics are of

great significance. They show the following: in uncomplicated gastric and duodenal ulcer there is a rise in mortality from 2.6 per cent (private cases) to 3.9 per cent (hospital cases). In Gavisser's reports the mortality in 416 resections in emergency cases is 4.5 per cent; in interval cases 3 per cent. Allen and Welch report a mortality of 5.1 and 2.5 per cent respectively, under similar conditions. Quite a low mortality percentage was achieved by Plenk. He and Stocker reported within a certain period of time 6 deaths in 641 cases, i.e., a mortality of 0.9 per cent. It would, however, be entirely fallacious, of course, to conclude from these reports when compared with the percentage of mortality subsequent to vagotomy that "in our cases therefore mortality not of vagotomy, but of gastric resection seems to be below 1 per cent."

The present report is a purely clinical one, avoiding comparison of any biochemical tests before and after operation, of x-ray studies or evaluation of the tests hitherto recommended (Hollander's insulin test, Mandl's test of paravertebral block). The problems advanced are simple: is it possible with a certain kind and location of peptic ulcer to avoid a dangerous and extensive operation? What results does vagotomy yield in such instances with respect to mortality and the subsequent course?

The special cases in which a dangerous gastric resection could be avoided, include: 1) the gastric ulcer near the cardia, and 2) the peptic ulcer of jejunum, designated in the American literature as stomal-ulcer and as marginal-ulcer.

*Ulcer near the cardia:* Finsterer in 1949 reported the largest series of cases operated upon for an ulcer near the cardia located in the lesser curvature. Of 614 cases of his, an arcuate or subtotal resection of the stomach was performed in 426 cases with a mortality of 10.3 per cent. According to Huber the scalariform subtotal resection of the stomach for gastric ulcer gives a mortality of 25 per cent. One may suppose that this operation was employed in the first place for ulcers near the cardia. As to Kelling-Madlenter's exclusion operation, it has been performed by Finsterer in 79 cases with a mortality of 5 per cent. If one considers the dubious value of this exclusion operation with regard to overlooking of malignancy and that it is, notwithstanding, associated with a relatively high mortality, an attempt at vagotomy in those cases is worthwhile with the similar risk as to possible mortality.

In these types of ulcer, total gastrectomy is to be shunned. Longmire reported deaths in 2 of 20 cases. Scott had a mortality of 9.5 per cent in 63 patients. Trimble and Lynn reported that survivors following this operation are to be designated undoubtedly as "stomach cripples" owing to the unfavorable results as seen on follow-up examinations. According to Welch and Allen, mortality following transthoracic total gastric resection was 31 per cent. Of 10 patients examined afterwards, 4 were reported as good results, 4 as fair ones, and 2 as failures.

A brief summary of parts of the case histories of ulcer near the cardia which merit attention follows:

*Case 1.* Josef H., born in 1891.

*Operation* (October 17, 1947). In the cardiac third of the stomach there was a penetrating ulcer which admitted 5 fingers of one's hand. The ulcer was soft with sharp shelving edges

and penetrated into the pancreas. A typical vagotomy was performed. The follow-up examinations showed continued improvement. On December 1, 1947, the ulcer niche, which had been of a mandarin's size before the operation, was already reduced to the size of a pea. X-ray studies on November 20, 1948 showed complete disappearance of the ulcer niche. The patient was quite well until May, 1949. In May, 1949 he took ill with appendicitis which went on to perforation. He was admitted to another hospital and died of peritonitis. Prof. Huber was kind enough to send us the specimen of the patient's stomach. In place of the preceding large ulcer there was a small ulcer in which a finger's head could scarcely be inserted. Nevertheless, it must be emphasized that the base of the ulcer was not covered with mucosa.

*Case 2.* Franz B., born in 1886.

*Operation* (October 23, 1947). A laparotomy revealed high on the lesser curvature in the cardiac third of the stomach an ulcer the size of about a finger's tip, surrounded by soft margins. As the patient's wasted general state did not allow a total gastric resection, a typical vagotomy was performed. Repeated examinations throughout the year of 1948 proved that he had no troublesome complaints at all. The examination on March 1950, showed the stomach to be perfectly normal. The patient was very pleased with the results of the operation.

*Case 3.* Wilhelm Ch., born in 1899.

*Operation* (November 17, 1947). High on the lesser curvature, in the cardiac third of the stomach there was a small ulcer with soft margins in which one can merely lay in one's little finger's tip. As a total gastric resection was not indicated for such a small ulcer, vagotomy was carried out. The last examination in December 1949 resulted in the patient's satisfaction with the operation.

*Case 4.* Leopold R., born 1884. The patient suffered from stomach trouble for 5 years. His general condition was poor. There were severe cachexia (37 Kg.) and a subicteric discoloration of the skin and mucosa. An x-ray examination disclosed a circular stenosing cancer with extensive ulceration on the lesser curvature.

*Operation* (October 29, 1947). A laparotomy revealed a crater-shaped ulcer the size of an infant's hand located high up on the lesser curvature. No glands or hepatic metastases were present. With the patient being unable to withstand any other operation, a vagus section was carried out. During the year 1948, the patient was repeatedly examined. His general state was a good one, gain in weight of 7 kg. X-ray of stomach showed no longer a niche nor a mural defect. The patient himself was satisfied with the results of the operation. Although he is strongly addicted to alcohol, he tolerated it at present without any pain. At the last examination in March 1950, the patient was quite well.

*Case 5.* Johann G., born in 1884.

*Operation* (March 23, 1948). Laparotomy revealed in the oral region of the cardiac part of stomach at its posterior wall an ulcer penetrating into the pancreas. Glands were found; both along the greater and lesser curvatures; their histological examination, however, was negative. A typical vagotomy was carried out. The postoperative course was fair. The patient's gastric complaints subsided at once, and he was able to eat everything. After having been discharged from the hospital in April, he had no trouble until August, when diarrhea occurred. In October he complained of pain in the right hypochondrium; at the same time jaundice developed, and he was admitted to the medical division. As the jaundice, however, increased markedly, consideration was given to the possibility of a stone occluding the common duct or the development of liver metastases. Therefore the patient was transferred to the surgical department.

*Second operation* (December 5, 1949). A transrectus laparotomy in the region of the right hypochondrium showed the stomach to be of normal size and tonus. The ulcer previously found on the lesser curvature near the cardia, was apparently cicatrized or very much reduced in size. The gall-bladder was altered by inflammation being closely adherent to the liver bed. Within the gall-bladder and common bile duct there was a great number of stones. A cholecystectomy followed by a choledochotomy with removal of the stones was carried out. Despite routine treatment, the patient died of pneumonia two weeks after



the operation. At postmortem, besides evidence of pneumonia, a pea-sized ulcer was found in the stomach just below the cardia.

*Case 6.* Anton M., born in 1900. For months the patient had had pain in the epigastric region, nausea and diarrhea appeared for the first time. Medical management yielded only transient improvement. On the night before hospitalization, hematemesis occurred followed by another one the next day.

*Operation* (July 5, 1948). The lesser curvature in the oral third of the stomach presented a fibrous ulcer where a finger could just be put in. A typical vagotomy was done. The course of healing was without complications. Continuous observation during 1948 and 1949 showed the patient to be completely free of complaints, of gastralgia and bleeding. A follow-up examination in March 1950 showed the same good state, with only slight meteorism after meals. He gained 7 kg. There was a small ventral hernia. The patient was satisfied with his condition.

*Case 7.* Johanna K., born in 1885. Gastric complaints for some time; the patient was admitted for acute gastric hemorrhage. Up to the operation she was given five blood transfusions.

*Operation* (July 20, 1948). A laparotomy revealed a tumor in the oral part of the cardiac third of the stomach, spreading into the region behind the body of the stomach. Into the area of penetration, 5 fingers of one's hand could readily be inserted. It was impossible to decide whether there was an ulcer or a cancer. The patient's general state was such that an extensive gastric resection was contraindicated, yet vagotomy was carried out and a posterior retrocolic gastroenterostomy added. During the year 1948 improvement was recognizable. The patient was able to digest all kinds of food and has gained 8 kg. in weight. There were neither hemorrhage nor troubles as to bowel function. On February 2, 1950 the patient died following a street accident.

*Case 8.* Franz U., born in 1894. He had had stomach complaints since April 1948. He was first admitted to the medical section for gastric hemorrhage. As the bleeding recurred to a much larger extent, the patient was transferred to the surgical department. Before being operated upon he received 7 blood transfusions.

*Operation* (January 11, 1949). Laparotomy revealed on the posterior of the stomach wall, just below the cardia, a soft ulcer with sharp edges surrounded by an inflammatory infiltration spreading to the lesser curvature. The question whether total gastric resection or vagotomy be done, was decided in favor of the latter. Vagus section was combined with ligation and suture of all the vessels to the ulcer.

The postoperative course was without complications. The patient had no pain. At the follow-up examination in March 1950 the patient stated that his restoration to well being was complete: he had neither gastralgia nor hemorrhage; occasional meteorism and eructations occurred and there was a tendency to diarrhea. He gained weight (3 kg.). He is working again being well satisfied with the results of the operation.

*Case 9.* D., physician, born in 1898. He had had stomach complaints since September 1943 and hematemesis in March 1944, when an x-ray examination detected a gastric ulcer.

*Operation* (May 2, 1949). At laparotomy a soft ulcer of evidently benign character just below the cardia at the minor curvature was found; there were no glands and the liver and gall-bladder were free. In order to avoid a total gastric resection, vagotomy was performed.

Despite the normal postoperative course the patient has not recovered since the operation. He continued to complain of a sensation of fullness, meteorism, lack of appetite, weakness, eructations and mental depression. In December 1949, he developed a pleuropneumonia and was transferred to the medical section of our hospital. Since hematemesis and melena occurred soon afterwards, the patient was returned to the surgical department. There he presented the following blood count: red blood corpuscles, 2,870,000; hemoglobin, 40; color index 0.7; leucocytes, 14,100. The patient was given blood transfusions.

*Second operation.* The stomach was markedly filled with air, but not dilated. Gastrotomy was performed in order to inspect the bleeding ulcer. The size and character of the ulcer were the same as on the first operation. An attempt was made to ligate all the vessels to the

ulcer, and the ulcer base itself and the stomach wall were sutured. Gastric resection was not considered because of the patient's poor condition and the height of the ulcer. The patient received 3000 cc. of blood before, during, and after the operation. He died twenty-eight hours postoperatively.

The postmortem findings showed that the bleeding had stopped. There had been an erosion of a branch of the left gastric artery. There were no signs of any recent hemorrhage, nor peritonitis. As an additional finding there was an abscess the size of a fist.

*Case 10.* Heinrich M., born in 1893. He was afflicted with stomach trouble since 1943.

*Operation* (May 1, 1948). Laparotomy revealed a small ulcer in the proximal third near the cardia. At the pylorus there was another small ulcer. A typical vagus section was carried out and was followed by a posterior retrocolic gastroenterostomy.

The postoperative course was without complications. A later examination, in March 1950, showed the patient to be in good health. He was well satisfied with the success of the operation.

*Comment.* From the foregoing it may be concluded that 10 vagotomized ulcers near the cardia gave the following results:

An excellent result in 7 cases. A fair result in 2 cases and a failure in one. There were no mortalities.

This experience permits one to infer that vagotomy for ulcer near the cardia yields good results as compared with those obtained from total or subtotal gastric resection, a procedure involving a greater risk. It may further be stated that there is lesser risk with vagotomy than with the Kelling-Mandlener operation.

*Peptic ulcer of the jejunum* (stomal-ulcer, marginal ulcer). The mortality of radical operation for jejunal peptic ulcer is high. Finsterer gives the following mortality statistics: in uncomplicated cases, 11.9 per cent; in those complicated by acute hemorrhage or gastro-jejuno-colic fistula, 40.8 per cent (Finsterer, 1949). According to Priestly and Gibson, the mortality of recurrent ulcers following gastroenterostomy ranges from 2.9 to 4.7 per cent, in peptic ulcer of the jejunum (stomal-ulcer, marginal ulcer) following gastric resection, the mortality is 11. It is no wonder, therefore, that vagotomy has been proposed by Dragstedt.

The results of vagotomy as a method of treatment of peptic ulcer of the jejunum are as follows: Priestly and Gibson had no deaths in 44 cases; 38 of these cases disclosed a satisfactory result at follow-up examinations. Walters and Brownson had good results with vagotomy in 8 of 10 cases (relapse following gastroenterostomy) and in 22 of 25 cases (relapses following gastric resections). Likewise in 4 cases of gastro-jejunal fistula, where the authors carried out a vagus section with simultaneous restoration of the normal anatomic status, there were good results. Grimson and his associates (1949), however, report fewer good results. Of 10 patients with relapsing ulcer following gastroenterostomy, only 5 recovered completely, whereas the remainder had still various complaints. Of 10 patients with recurrent ulcers following gastric resection, 5 had complete restoration, while 4 patients had various complaints. Colp (1947), generally an opponent of vagotomy, is of the opinion that its best results are those obtained in gastro-jejunal ulceration. He obtained perfect results in 4 cases of this type of ulcer following gastroenterostomy as well as in 11 cases of gastric resection. The severe pains subsided immediately, the acid output regressed, and x-ray

TABLE I  
*Vagotomy for ulcers near the cardia*

NR.	AGE, IN YEARS	SUFFERING WITH STOMACH TROUBLE FOR	DATE OF VAGOTOMY	RESULT AND DATE OF THE FOLLOW-UP EXAMINATION	NOTES	RESULTS
1	56	11 years	Oct. 17, 1947	April 1949: quite free from pain; the patient is well	May 1949: Death. Perforation of appendix $\bar{c}$ peri- tonitis. The ul- cer is small, un- covered with mucosa.	Excellent
2	61	6 years	Oct. 23, 1947	March 1950: quite well as to stom- ach; no diarrhea. Pat. is very sat- isfied with the operation	Suffering from pulmonary tu- berculosis	Excellent
3	48	7 years	Nov. 17, 1947	December 1949: to- tally free of com- plaints; tole- rating any food, now and then diarrhea which does not trouble him. 5 kg. gain of weight		Excellent
4	63	5 years	Oct. 29, 1947	March 1950: The patient is well	Addicted to Alco- hol	Excellent
5	64	5 years	March 23, 1948	Oct. 1949: stomach well	Death after Choledochotomy	Fair
6	48	Hema- temesis	July 5, 1948	March 5th: free of complaints, 7 kg. gain in weight		Excellent
7	63	Hema- temesis	July 2, 1948	December 1948: very well	1950 Death from an accident	Excellent
8	55	5 months	Jan. 11, 1949	March 1950: quite free of pain. Now and then meteorism and eructations. 3 kg. gain in weight	Very satisfied with with the opera- tion. Resumed his work	Fair
9	51	6 years; hema- teme- sis	May 2, 1949	No improvement; death of gastric hemorrhage on Dec. 13, 1949		Failure
10	56	6 years	May 5, 1948	March 1950: ex- cellent state		Excellent

TABLE II  
*Vagotomy for peptic ulcer of jejunum*

NR.	AGE AT OP.	YEAR OF GASTRIC RESECTION	SUBSEQUENTLY WELL FOR:	DATE OF VAGOTOMY	POST-OP. COURSE	RESULT AND DATE OF FOLLOW-UP EXAMINATION	RESULT
1	56	1944	3 years	Nov. 19, 1947	Death	Died of meningitis	—
2	37	1936, 1937 1938, 1940	About 3 months each time	Dec. 1, 1947	fair	Unsuccessfully operated upon in another department "Surgically incurable ulcer"	Failure
3	50	1945	1 year	Jan. 9, 1947	fair	March 50: Entirely free of distress	Excellent
4	47	1942	3 years	Jan. 17, 1948	fair	July 49: Well up to this date; now has recurring complaints as prior to operation	Failure
5	36	1941	2 years	March 17, 1948	fair	Dec. 48: Hitherto well then recurrent gastric hemorrhage. Op. on another service	Failure
6	35	1942	5 years	May 3, 1948	fair	March 50: Very good state	Excellent
7	58	1929	19 years	April 27, 1948	fair	Jan. 49: Died of cancer	—
8	25	1947	1 year	July 10, 1948	fair	March 50: Well	Excellent
9	34	1941	7 years	July 16, 1948	fair	March 50: Entirely well	Excellent
10*	54	1919	28 years	Aug. 48. Partial vagotomy	fair	Jan. 49: No success; death following radical operation on another Service	Failure
11	36	1936	6 years	Nov. 5, 1948	fair	March 50: Entirely well	Excellent
12	67	1918	25 years	Feb. 23, 1949	fair	Death of pneumonia 1 month post-op.	?
13	35	1946	2 years	May 15, 1949	fair	March 50: Entirely well	Excellent
14*	56	Gastroenterostomy in 1916	13 years	Sept. 14, 1949	fair	Nov. 49: Death of hypoproteinemia	?

\* Gastro-colic fistula.



examination disclosed no signs of ulcer. The postoperative course was fair in all instances.

Brief abstracts of case histories of patients with peptic ulcer of the jejunum which occurred following gastric resection or gastroenterostomy follow.

*Case 1.* Franz B., born in 1891. The patient had undergone an operation in a Vienna hospital on December 16, 1944. After the operation he was quite well until early 1947.

*Operation* (November 19, 1947). The stomach presented adhesions; its stump was of medium size. The anastomosis was patent. At the lesser curvature there was a simple ulcer near the anastomosis. Vagotomy was performed.

After an uneventful postoperative course in the beginning, the patient died of purulent meningitis 10 days after the operation. The pathologist found greenish yellow pus covering the whole surface of the brain and on the cerebellum, and thought that it originated from a sinusitis. The findings in the stomach were the same as noted at the operation.

*Case 2.* Franz L., born in 1910. The patient was operated upon in 1936, in a Vienna Clinic according to Billroth's Method II. Three months later symptoms reappeared. A peptic ulcer of jejunum was diagnosed. The patient was operated upon in the same clinic in 1937, a stomach resection of the Billroth I type being performed. Six weeks later the former complaints reappeared. In May 1938 hematemesis occurred. He was once more operated upon in the same clinic in October. The next gastric operation was carried out upon this patient in 1940. In August of the same year he developed a strangulation ileus and was once again operated upon. After his discharge he had continuous gastric complaints. X-ray examination in 1945 revealed signs of peptic ulcer of jejunum.

*Operation* (December 1, 1947). The stomach stump showed a soft defect of about a lentil's size at the lesser curvature. We were dealing with a simple ulcer. The stump of the stomach was small. The anastomosis was fairly patent. Between the gall-bladder and duodenum there were numerous adhesions. Typical vagotomy was performed.

Fair postoperative course. The patient was discharged in an improved state 3 weeks after the operation. The improvement, however, lasted only about 2 months. In April 1948 the patient was admitted to the surgical division I of the Allgemeines Krankenhaus (Prof. Finsterer) where another laparotomy was performed. By the use of gastrostomy, Finsterer was able to ascertain the absence of the relapsing ulcer, met with and described at the previous operation. Owing to the negative result of exploration cholecystectomy was performed. He felt fairly well after it, but the improvement in his condition lasted only 3 weeks. His present status is unknown.

*Case 3.* Mendel T., born in 1897. In 1945 he had undergone extensive gastric resection for gastric ulcer in Budapest. For one year he was in good health and free of complaints. An x-ray examination disclosed a peptic ulcer of jejunum (stomal ulcer, marginal ulcer).

*Operation* (January 1, 1947). At laparotomy a small stump of stomach was found. The anastomosis was patent. In the jejunum, at the ring of the anastomosis there was a small, hard, round peptic ulcer. Typical vagotomy was performed.

Follow-up examination in March 1950. The patient was quite well.

*Case 4.* Leopold V., born in 1901. In 1942, gastric resection for duodenal ulcer according to Billroth's Method II was done at another hospital. In 1943, he was operated on for a cicatricial hernia. In 1945, he was given two series of *Larostidin* for relapsing gastric troubles. Six months prior to admission to our division, stomach complaints occurred anew.

*Operation* (January 17, 1948). Laparotomy revealed but few adhesions. The gastric stump was small and the anastomosis which was of the retrocolic type was patent, admitting at least two fingers. At the edge of the anastomosis towards the liver, an ulcer was encountered. The serosa over it was of a fiery red color. Typical vagotomy was performed.

Fair postoperative course. The patient was quite well until July 1949. A later examination in March 1950 showed that the patient had the same complaints as before operation. An x-ray examination did not detect any abnormalities.

*Case 5.* Michael L., born in 1912. In 1941, he had undergone gastric resection for duodenal ulcer at another hospital. For 2 years postoperatively the patient was in quite good health. Then there recurred gastric hemorrhages. Owing to his anemia he was prepared for operation with several blood transfusions.

*Operation* (March 17, 1948). There were moderate adhesions. It was evident that a gastric resection according to Billroth's Method I had been performed. At the site of anastomosis between the gastric stump and duodenum, at the lesser curvature there was an ulcer of thumb size which felt very fibrous and over which the serosa was of fiery red color. Typical vagotomy was performed.

Fair course of healing without complications. Until December 1948 the patient felt well. On December 24, 1948, a severe gastric hemorrhage occurred. He was therefore admitted to another surgical division where he was operated upon. The result of this operation is not known.

*Case 6.* Anna K., born in 1913. The patient had had stomach complaints since the age of 13 years. In 1942 an operation according to Billroth's Method II was carried out at another division. She was well till the autumn of 1947 when her old complaints recurred.

*Operation* (May 3, 1948). The small gastric stump presented a peptic ulcer of the jejunum at the junction between the site of resection and the anastomosis; the ulcer extended from the side of the lesser curvature spreading into the anastomotic ring. Typical vagotomy was performed. The operative course was fair. In December 1948, the patient developed the symptoms of hypophyseal tumor with marked limitation of the field of vision. In December 1948, she was successfully operated on for an hypophyseal adenoma at the Surgical University-Clinic I (Prof. Schönbauer). Last follow-up examination in March 1950. No gastralgia; the patient is on a full diet; gain in weight of 9 kg.

*Case 7.* Maria D., born in 1890. In 1929, I performed a gastric resection for gastric ulcer at Hohenegg's Clinic according to the method of Hofmeister-Finsterer. The patient was well until 1947. For half a year she was again having trouble with her stomach. Her body weight was 35 kg. X-ray status following gastric resection. The anastomosis was scarcely open. The outline of the stump of stomach above the anastomosis was rigid and had irregular boundaries. The patient was prepared for operation by several blood transfusions.

*Operation* (April 27, 1948). The stump of stomach was found to be very small. The anastomosis was not patent as almost exactly at the anastomotic ring a nearly circular ulcer encroached upon the efferent loop of the anastomosis. The ulcer was a very extensive one. The liver and gall-bladder were free. There were no glands. Since no other operation could be carried out on the very debilitated patient, vagotomy was performed and because of the stenosis gastroenterostomy was added.

Normal postoperative course. Until August 1948 the patient recovered slowly. Though the patient was on a full diet, the gain in weight was only half a kg. In December she was again admitted for pain, nausea and vomiting. She was very emaciated, vomiting all ingested food. There developed ascites, hydrothorax and marked edema of the legs. Thoracocentesis did not reveal any tumor cells. Plasma transfusions were given. Death occurred on January 29, 1949.

*Postmortem findings.* There was an ulcerated medullary cancer spreading into the stump wall and perforation into the left subphrenic region. There were adhesions between the stomach and the porta hepatis and the diaphragm. The anastomosis carried out a few months ago was not remarkable.

*Case 8.* Leopold S., born in 1922. History of duodenal ulcer since 1945.

*Operation* (January 28, 1947). At a finger's breadth beyond the pylorus there was a small hard ulcer. The duodenal ulcer was resected according to Hofmeister-Finsterer removing two thirds of the stomach and carrying out a retrocolic anastomosis. The patient was discharged in February free of complaints. He felt well until April 1948. Then he began to complain of spasmodic pain in the epigastric region occurring after meals and of vomiting. An x-ray study aroused the suspicion of a new ulcer.

*Second operation* (July 10, 1948). The gastric stump was of medium size; the anastomosis admitted readily 2 fingers. At the anastomotic ring a round hard ulcer was found into which a finger could be inserted. Typical vagotomy was performed.

Soon after the operation the patient had a good appetite being on a full diet. Follow-up examination in March 1950, disclosed that since the operation he was entirely free of pain on a full diet and gained in weight.

*Case 9.* Aloisia K., born in 1914. She had had a gastric resection (Billroth's Method II) for a gastric ulcer in 1941, on another service. She remained well until the Spring of 1948, when her gastric symptoms recurred.

*Operation* (July 16, 1948). There were extensive adhesions between stomach stump, liver and abdominal wall. At the border between the stump of the stomach and the anastomosis, an ulcer was seen, into which a thumb could be inserted. It was exposed by means of a gastrotomy. The anastomosis was not stenosed. Vagotomy was performed.

The postoperative course was without any complications. Follow-up examination in March 1950, showed that the patient has had no complaints, gained in weight, and was satisfied with the results of the operation.

*Case 10.* Hans. S., born in 1894. Twenty-nine (?) years ago had had a gastric resection (Billroth's Method II) for an ulcer. He felt well until 1947, then severe symptoms with anemia as the predominating finding set in. X-ray studies revealed the stomach to be small. There was a lesion the size of an apple. No decision could be made whether it was a neoplastic or an ulcerative process. The patient was given blood transfusions.

*Operation.* After division of the adhesions, a fist-sized tumor was observed at the anterior wall of the stomach stump, extending widely into the jejunum and penetrating towards the transverse colon. It was considered to be a peptic ulcer of the jejunum; differentiation from a cancer was not certain. As the patient was not able to undergo any other operation, vagotomy was attempted. The lumbar anesthesia under which the operation was performed seemed to be ineffective in the field of the vagal branches as the patient was complaining of pain in the region of the esophagus at the touch of the anterior vagus which was readily removable. Despite a long search for the posterior vagus branch, it could not be exposed, and therefore was not removed. The patient refused additional ether narcosis, and the operation had to be terminated because of the induced pain.

The first postoperative days were satisfactory and recovery took place during the following weeks. In October he felt better than prior to operation, the blood count, however, showed fluctuation and, since tests for occult blood were positive, the patient was given blood transfusions. In November 1948, an x-ray examination showed the tumor detected previously to have decreased in size, being seen now merely as a small niche. During the months of November and December, 1948 the patient's gastric complaints became markedly worse. In January 1949 he came under the care of another surgeon who performed a resection of the stomach, the small and the large intestine for the cure of a peptic ulcer of the jejunum. The patient died 48 hours after the operation.

*Case 11.* Franz B., born in 1912. He had a gastric resection for duodenal ulcer done in another hospital, in 1936. He felt well until 1942, when the gastric complaints recurred. X-ray studies suggested the presence of an ulcer.

*Operation* (November 5, 1948). A laparotomy showed that the first operation had been carried out according to Billroth's Method II. On the posterior wall of the anastomosis between stomach and duodenum, there was a pea-sized ulcer into which one finger could be inserted: a typical anastomotic ulcer. Vagotomy was performed. The postoperative course was fair. In March 1950, he was found to be well as far as his stomach was concerned but was said to have a psychosis.

*Case 12.* Ludwig R., born in 1882. The patient had had a gastric resection for a gastric ulcer at another hospital, in 1918. X-ray studies revealed a niche above the anastomosis. Malignant degeneration could not be excluded.

*Operation* (February 23, 1949). After dividing the adhesions, it became apparent that the previous resection had been performed according to Billroth's Method II. The anastomosis



was patent. On the lesser curvature of the stomach, at some distance from the anastomosis, there was an ulcer; its malignant degeneration could almost be excluded. Typical vagotomy was performed, with a fair postoperative course. In March symptoms of prostatic hypertrophy appeared; "a sectio alta" was carried out. As for his stomach, the patient was discharged in good condition. On April 27, 1949, he was again admitted to the hospital for pneumonia, of which he died at the end of a week.

*Case 13.* Johann S., born in 1914. He had had a gastric resection performed in another department, in 1936. For the following 2 years he was well. Since November 1948, he complained again of a stomach disorder.

*Operation* (May 15, 1949). There was a comparatively large gastric stump. The anastomosis was patent, admitting two fingers. At the site of the lesser curvature of the stomach there was a small, flat ulcer. Typical vagotomy was performed.

The postoperative course was fair. Follow-up examination in March 1950, showed that except for indigestion in September 1949, he has not had any more gastric complaints. He gained weight and was well satisfied with the results of the operation. He has had two soft stools daily, which, however, did not trouble him.

*Case 14.* Heinrich W., born in 1893. The patient has had a gastroenterostomy in 1916. In 1929, 1932, 1942, and 1949, he had recurrent gastric hemorrhages. In 1948, a gastro-colic fistula had been established. Subsequently he developed diarrhea, loss in weight and ascites. In August 1949, the patient was hospitalized in a very poor condition, suffering from hypoproteinemia. Severe diarrhea, edema of the lower limbs with marked ascites developed. Preoperative management with plasma and vitamins.

*Operation* (September 14, 1949). The previous site of anastomosis between stomach and small gut was found to be obstructed by an ulcerated tumor. Upon digital examination the stomach could be entered from the jejunum as well as the transverse colon from the jejunum. There is thus a gastro-jejuno-colic fistula. Owing to the patient's emaciated state, vagotomy was carried out to which an anterior antecolic gastroenterostomy was added. No complaints followed the operation, yet the edema continued to increase during the month of October. The patient died on November 1, 1949 with the signs of severe hypoproteinemia, extensive edema of the entire body, nausea, weakness and anorexia. Necropsy revealed an extensive peptic ulcer of the jejunum in the region of the old anastomosis penetrating into the transverse colon. The anastomosis carried out 6 weeks previously was functioning. There were about 3 litres of ascitic fluid, hydropericardium, hydrothorax, and pulmonary edema.

*Comment.* A survey of the appended table II, which is a synopsis of vagotomized cases of peptic ulcer of the jejunum, shows success in 6 instances, a failure in 5 instances and one postoperative death. Two cases thus remain unevaluated (Cases 12 and 14).

Of the 14 cases of peptic ulcer of the jejunum (stomal-ulcer, marginal-ulcer) or recurrent ulcer, only one of these followed a gastroenterostomy performed 33 years ago. In 13 instances, the peptic ulcer of the jejunum had developed following a gastric resection. Three patients had undergone these resections very long ago: one, 31 years (Case 12), the other, 30 years (Case 10) and the third, 20 years ago (Case 7).

In general it can be said that my material as such includes some very unfavorable types. One of our 3 deaths belongs to this group (Case 1). Moreover, in this case, the presence of gastro-colic fistula further complicated matters. In one instance (Case 10), failure has been caused by the impossibility of carrying out a complete vagotomy, in another (Case 14) by so severe a hypoproteinemic state of the patient upon his admission that in spite of medical therapy improvement was impossible. Another circumstance contributing to failure is the fact that in



Case 2 we are dealing with what I call "surgically incurable ulcer" (Mandl), or a so-called "surgically difficultly curable ulcer" (Finsterer). Such cases occurring again and again in the literature derange any statistics on gastric operations. A special situation exists in Case 7, in which, after a gastric resection that I performed myself in 1929, and 19 years had elapsed, an apparent peptic ulcer developed within the anastomosis which at necropsy turned out to be a cancer.

Nevertheless, on the basis of the operative results I have obtained with vagotomy in the treatment of peptic ulcer of the jejunum, it may not be concluded that the operation might not be efficacious in this type of ulcer. In this regard statements in the literature seem decisive: vagotomy is less dangerous than the radical operation, and yields success in a high percentage of cases.

#### SUMMARY

Of 250 vagotomies carried out for gastric ulcer, pyloric ulcer, duodenal ulcer, peptic ulcer of the jejunum (stomal-ulcer, marginal-ulcer), and also as an analgesic operation for gastric cancer etc., three cases died, (meningitis, massive pulmonary embolism, cardiac death). Of this series of operations, 10 cases of ulcer near the cardia are discussed first. None of the patients died of the operation. The results of the follow-up examination are as follows: The operation yielded an excellent result in 7 instances, in two cases the result may be evaluated as fair, while in one case vagotomy is to be considered a failure as the patient died of gastric hemorrhage 7 months following operation.

In this material, likewise 14 cases of peptic ulcer of jejunum (stomal-ulcer, marginal-ulcer) were singled out in which the peptic ulcer had arisen in 13 instances subsequent to gastric resection and once only following gastroenterostomy. In 3 cases primary gastric resection had taken place very long ago (one case, 31 years, another, 30 years, a third one, 20 years ago). One of these cases died of meningitis for which the etiology could not be found at necropsy (sinusitis?).

The follow-up examination of the patients showed: of 13 cases, failures occurred in 5, in which, however, not all, can be ascribed to the operation. One of these 5 cases was a so-called "surgically incurable ulcer." Prior to vagotomy this patient's stomach had been operated upon unsuccessfully 4 times. Another case in this series was well for 19 months, but then the previous complaints recurred. In the third case reoperation had to be carried out for gastric hemorrhage on another service. A further case was not improved by vagotomy for the reason that during the operation only the anterior vagus could be removed. Subsequently he was radically operated upon in another department, surviving this operation only 48 hours. The fifth case finally presented a gastro-jejuno-colic fistula following gastroenterostomy, the patient being admitted in such a hypoproteinemic state that recovery after operation was impossible.

In 6 instances, however, the result of vagotomy was an excellent one. It could scarcely be surpassed by a radical operation.

Two cases do not permit evaluating for vagotomy for one patient died of pneumonia after one month had elapsed postoperatively, while another one died

a few months after vagotomy had been performed of a cancer which had been supposed to be a recurrent ulcer.

For these reasons conclusions are as follows: that for ulcers near the cardia vagotomy is to be preferred to total or subtotal gastric resection. Furthermore, the results in uncomplicated cases of recurrent ulcer following gastric resection are particularly good, provided the general condition of the patient is not too poor.

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# VAGOTOMY AND SUBTOTAL GASTRIC RESECTION WITH VAGOTOMY IN CASES OF GASTROJEJUNAL AND GASTROJEJUNOCOLIC ULCERS AND FISTULAS AFTER MULTIPLE PREVIOUS SURGICAL PROCEDURES

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Our two cases illustrate well the feasibility and advantages of further surgical procedures when gastrojejunal or gastrojejunocolic ulcers and fistulas recur despite multiple previous operations including several partial gastric resections. Moreover they demonstrate the availability of the vagus nerves for transabdominal resection in such cases even though resection of the nerves was thought to have been carried out.

Vagotomy appears to be an operation of choice for the rare gastrojejunal ulcer which follows properly performed adequate gastrectomy for duodenal ulcer (1, 2). Supradiaphragmatic vagotomy has been favored by some surgeons in cases in which a gastrojejunal ulcer develops subsequent to subtotal gastrectomy (3). Transabdominal vagotomy, however, permits exploration of the resected stomach and the anastomosis and performance of required procedure on the stomach and intestines. In these cases in which past events would lead one to expect more than average difficulty, the abdominal approach was used with considerable advantage for it permitted correction of the pathologic condition with simultaneous vagotomy.

## REPORT OF CASES

*Case 1.* On October 27, 1948, the patient, a man of 50 years, who was an aviation mechanic, first registered at the Mayo Clinic. He presented a long history of peptic ulcer with onset of symptoms in 1927. In the next six years he experienced melena three times. In 1934 and again in 1935, acute perforation of duodenal ulcers required surgical closure. He then was fairly well until March, 1947, when recurring hematemesis and melena led to partial gastric resection on May 31, 1947. After this operation a constant gnawing pain troubled him. On December 25, 1947, severe back pain developed and persisted intermittently until March, 1948. At an operation on March 12, 1948, two marginal ulcers (one perforated) were demonstrated and a second partial gastric resection and vagotomy were reported. All these operations were performed before the patient registered at the Clinic. A constant mid-abdominal pain, not related to food or bowel movements, followed the operation in March, 1948. The patient was easily upset and cried readily. Finding that regurgitation resulted from the eating of solid foods, he reduced his diet to custards, scallops and 4 quarts (4,000 cc.) of milk daily. Examination, including gastroscopy, prior to his coming to the Clinic gave negative results.

On examination at the Clinic in October, 1948, the patient was found to be a thin, well-developed man with multiple abdominal scars; he was rather depressed and in an anxiety tension state. Roentgenologic study showed the gastro-intestinal anastomosis to be free and functioning well. Study of gastric contents revealed 22 units of total acid and 12 units of free hydrochloric acid (Töpfer's reagent). Psychiatric counsel relieved much of his

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anxiety and depression. He began to eat better after dietary instruction. When he was dismissed, he was feeling well, and was taking three meals of high caloric content a day.

On December 22, 1948, the patient experienced severe pain in the left costovertebral angle and in the left lower quadrant of the abdomen which required a hypodermic injection for relief. Thereafter diarrhea consisting of ten stools daily lasted two days, then it recurred four days later. The pain recurred December 30. A fecal odor was noted on the breath, and undigested particles of food were seen in stools. The patient was hospitalized at home January 1, 1949, and was given two transfusions of blood. He returned to the Clinic January 17. A gastrocolic fistula was demonstrated in the roentgenogram and a Hollander insulin test gave a positive result (table 1).

On January 24, 1949, operation was performed by one of us (Walters) through a primary transverse abdominal incision. A huge perforating gastrojejunocolic ulcer was found with a crater measuring 7.5 cm. in diameter. There were three separate fistulous openings in the transverse colon resulting from perforations of the ulcer to the anterior abdominal wall, the pancreas, and the liver. The anterior Polya-Balfour anastomosis was disconnected. Fistulous openings in the colon were closed with a single row of interrupted silk sutures and protected with omentum. The perforation in the posterior wall of the jejunum was closed and the jejunum was reconstructed with a single row of sutures posteriorly. A cuff of gastric wall 2.5 cm. in width was excised and a loop of jejunum about 20 cm. from the

TABLE 1  
*Case 1: Insulin tolerance test, January 20, 1949*

TIME IN MINUTES	BLOOD SUGAR, MG. PER 100 CC.	GASTRIC CONTENTS		
		Volume in cc.	Free HCl, units	Total acid
Before injection	94	20	0	8
After injection				
15	59	10	0	10
30	40	8	0	12
45	38	15	0	12
60	41	20	60	80

ligament of Treitz was used to restore the anterior Polya-Balfour anastomosis. A temporary jejunostomy, using a number of 18 F. catheter, was performed. A loop of transverse colon near the hepatic flexure and proximal to the closed fistulous openings was brought out of the abdomen over a glass rod; this was opened four days after operation as a temporary colonic stoma.

The postoperative convalescence was uneventful. Intravenous and jejunal feedings were supplemented on the sixth postoperative day by the oral intake of food recommended after gastric surgery. The diet was progressively increased. The jejunal tube was removed sixteen days after operation, and the colonic stoma was closed at operation on February 25, 1949 (thirty-three days after operation).

The patient began to note some abdominal soreness and several black stools in February, but no ulcer type of pain. The problem of recurrent ulceration was considered, medical ambulatory management and the possibility of transthoracic vagotomy being contemplated. An insulin test on February 18, 1949, was interrupted because of severe insulin reaction, the partial results being termed equivocal. On March 6, 1949, he was dismissed from the Clinic. After an extended vacation in Florida, he returned to work on May 2, 1949.

On May 25, 1949, he came again to the Clinic, because of severe pain in the left upper quadrant with some posterior extension for the preceding ten days. Hypodermic injections were required for relief. He also noted a little diarrhea with foul-smelling stools. Results of an insulin test were positive and roentgenograms demonstrated a gastrojejunal ulcer.

Transthoracic vagotomy was advised, but reluctance on the part of the patient with regard to further surgery led instead to a trial of roentgen treatment of the stomach. This afforded relief which, however, was felt to be temporary. The patient was discharged on June 27, 1949, with instructions to continue with a medical regime.

On August 20, 1949, he re-entered the Clinic because of boring, gnawing abdominal pain and diarrhea for the preceding sixteen days. Examination disclosed the abdomen to be tender in the left upper quadrant. Roentgenologic examinations revealed a large gastrojejunal ulcer, and a gastro jejunocolic fistula high in the subdiaphragmatic portion of the abdomen. Gastric contents contained a total of 12 units of acid and 0 units of free hydrochloric acid. The value for hemoglobin was 9.3 gm. per 100 cc. and for total serum proteins 5 gm. per 100 cc. The albumin-globulin ratio was 3.8 to 1.2. Two transfusions of 500 cc. of blood each were administered.

On August 29, 1949, through a secondary transverse epigastric incision, a large, perforating gastrojejunocolic ulcer was found on the posterior wall at the site of the anastomosis. The ulcer was 4 cm. in diameter with a crater 2.5 cm. in diameter. The structures were separated. The opening in the colon (2 cm. in diameter) was closed with two rows of chromic catgut and an outer row of silk with a protecting layer of omentum was sutured over this. Because of the extent of the ulceration, the involved section of jejunum was resected and an end-to-end anastomosis of the jejunum was made. It proved feasible to free up the esophagus, and a large (5 mm.) posterior vagus nerve and an anterior vagus nerve (2 mm.) were found. These were divided and sections of nerve 2.5 cm. in length were removed. The sections were confirmed as being nerve tissue by the pathologist. Most of the remaining stomach (a segment 10 cm. in length) was removed and an anterior Polya-Balfour anastomosis was made by using a rather long (25 to 30 cm.) proximal loop of jejunum. The right portion of the transverse colon, still attached to the anterior abdominal wall at site of the former colostomy was left undisturbed for possible use as a temporary colonic stoma.

The postoperative course was uneventful. The patient was given supplementary transfusions of 500 cc. of whole blood each, on the ninth and eleventh postoperative days. He was dismissed from the hospital on the thirteenth postoperative day. Roentgenologic examination on September 14 showed that almost complete gastrectomy had been performed (fig. 1) and the anastomosis to the jejunum was functioning normally. Because of previous reactions, he would not consent to another insulin test, but an attempt to obtain gastric secretion for analysis showed no such secretion present on September 14. Unauthorized and indiscreetly, he did eat at one meal a shrimp cocktail, steak and apple pie à la mode on the fifteenth postoperative day and suffered no distress from it. On September 15, 1949, (18 days after operation) he insisted on going home. At that time he felt remarkably well and was in good general condition.

*Case 2.* A shoe salesman, 46 years old, registered at the Clinic September 3, 1949. In 1934 he experienced pain in the epigastrium, when the stomach was empty. Night pain was a feature. Relief was obtained by taking food or alkaline medication. In the fall of 1934, an episode of hematemesis and melena occurred. By use of a liberal ulcer diet given by his physician, he did well until 1936. In that year an acute perforation of the appendix and acute perforation of a duodenal ulcer developed simultaneously for which he was operated on elsewhere. In a stormy postoperative course he lost 60 pounds (27.2 kg.) in three months. Epigastric pain persisted in troubling him thereafter. Periods of hematemesis and melena were noted in 1938, 1939, 1945, and 1946. In July, 1946, partial (two-thirds) gastric resection was performed elsewhere, and was complicated postoperatively by a subphrenic abscess. Several transfusions of blood and plasma were employed.

In January, 1947, (5 months after operation) the patient had the first spell of jaundice which lasted two or three days. This was followed every two months by attacks of jaundice, lasting two or three days; the jaundice occasionally was accompanied by upper abdominal pain. In the spring of 1948, there began episodes of chills and fever, with interscapular aching, taking place five or six times yearly. The patient noted no relation between the chills and periods of jaundice.

In July, 1948, the patient had a sudden recurrence of ulcer type of pain and one week later severe melena. In August, 1948, a perforated marginal ulcer was closed and anastomosis of the stomach and jejunum was re-established. At that operation done elsewhere, stones were removed from the cystic duct through the gallbladder. The spells of jaundice continued, however. In January, 1949, pain in the right upper quadrant led to hospitalization



FIG. 1. Almost complete gastrectomy has been performed for multiple recurrent gastro-jejunal ulcers and fistulas.

for a week. He felt run down through the next eight months. In August, 1949, three weeks before admission to the Clinic, continuous sharp pain developed in the left upper quadrant. Jaundice recurred one week before admission. In addition to the sharp pain, seven or eight attacks of very severe pain also occurred daily in the same region.

Examination on admission to the Clinic September 3, revealed an asthenic man with

icterus, grade 2 (on a grading basis of 1 to 4). The edge of the liver was felt 2 fingerbreadths below the right costal margin. High in the left upper quadrant was an area of local tenderness, grade 3, and resistance, suggestive also of a small mass. Laboratory studies revealed 12.3 gm. per 100 cc. of hemoglobin, a sedimentation rate of 104 mm. in one hour, prothrombin time of 20 seconds, 47.4 units of alkaline phosphatase (Bodansky) per 100 cc. of serum. The value for direct reacting serum bilirubin was 6.8 mg. per 100 cc. and for the indirect reacting type 0.4 mg. The value for serum lipase was 0.4 cc. of tenth normal base per cubic centimeter; of total proteins 8.5 gm. per 100 cc., but with an albumin-globulin ratio of 3.9 to 4.6. There were 66 units of total acid and 52 units of free hydrochloric acid in the gastric contents. Roentgenograms revealed jejunitis with a gastrojejunal ulcer. The diagnosis was common duct stone and marginal ulcer. Treatment contemplated was exploration of the common duct and vagotomy.

On September 12, 1949, a tertiary right upper rectus incision was made and part of the old scars of previous operations were excised. A very large common bile duct was exposed; it measured approximately 2 cm. in diameter and was filled with stones and stony debris of the bile pigment type. The largest stone was 2 cm. in diameter. Much yellow, mushy debris was present in the intrahepatic ducts. After removal of the stones from the ducts,

TABLE 2

*Case 2: Insulin tolerance test, September 29, 1949*

TIME IN MINUTES	BLOOD SUGAR, MG. PER 100 CC.	GASTRIC CONTENTS		
		Volume in cc.*	Free HCl, units	Total acid
Before injection	84	12	0	10
After injection				
15	65	8	0	12
30	45	7	0	10
45	45	12	0	10
60	40	6	0	8
75	45	10	0	10
90	51	10	0	10

\* Twelve-hour gastric secretion contained 12 units of total acid and no free hydrochloric acid.

it was found that a 2 mm. probe passed with difficulty through the sphincter of Oddi. This was dilated with a 4 mm. probe, a 4 mm. scoop and an 8 mm. scoop. A considerable degree of thickening was felt in the pancreas surrounding the common bile duct. There did not appear to be any encroachment of the closed end of the duodenum on the common duct. Thorough irrigation of ducts and removal of debris was done. A number 20 T tube was sutured into the common duct. The gallbladder was not removed because of the possibility that cholecystoduodenostomy might be needed in the future if the pancreatic portion of the common duct again should become obstructed. Hepatitis, grade 3, and pancreatitis, grade 3+, were noted.

A large perforated gastrojejunal ulcer in the anterior wall at the site of the anterior Polya-Balfour anastomosis in a twice-resected stomach was attached to the abdominal wall. The ulcer was 4 cm. in diameter with a 2.5 cm. crater. In order to expose the vagus nerves, the ulcer was detached and closed with interrupted sutures of chromic catgut and silk, protecting it with omentum. The esophagus was then exposed and three vagus nerves found: one posterior 4 mm. in diameter, and two anterior, the left anterior 3 mm. and right anterior 1 mm. in diameter. Sections of the three nerves 2.5 cm. in length were removed. In closing the wound a previously formed incisional hernia was repaired.



Postoperatively, the course was relatively smooth; electrolytes were controlled well with intravenous solutions and the early oral use of a high protein diet. A small area of superficial wound separation at site of old scar tissue healed satisfactorily. On September 27, 1949, the concentration of hemoglobin was 13.1 gm., of serum bilirubin, direct reacting 2.7 mg., indirect reacting 0.9 mg., and of total proteins 7.8 gm. The T tube was clamped without pain all day except immediately after meals by the seventeenth postoperative day.

An insulin test gave negative results on September 29 (table 2).

A cholangiogram on October 3, 1949, demonstrated dilated common and hepatic ducts, with a small amount of medium entering the duodenum. The patient was dismissed in good condition on October 6, 1949. The T tube was to be removed one month after dismissal.

#### SUMMARY AND COMMENTS

In Case 1, five operations (the fourth and fifth at the Clinic) directed toward correcting peptic ulceration and its effects had been done before almost total gastrectomy and vagotomy were performed. Multiple perforations, including three separate fistulous openings in the transverse colon with a huge perforating gastrojejunocolic fistula, found at operation in January, 1949, complicated the situation. At his latest operation he presented the difficulty of recurring gastroenterocolic fistula high in the subdiaphragmatic portion of the abdomen. The second patient had had three previous operations (closure of acute perforations, partial gastric resection, and closure of perforated marginal ulcer with anastomosis of the stomach and jejunum and removal of stones through the gallbladder). He also had had a subphrenic abscess. At operation at the Clinic the common duct was found to be obstructed by stones, and a large perforated gastrojejunal ulcer was present in a twice-resected stomach.

In both cases it proved possible to resect the vagi without undue difficulty and reconstruct the gastrojejunal anastomosis, in one case after almost total gastrectomy.

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# OBSERVATIONS ON GASTRECTOMY FOR CHRONIC DUODENAL ULCER WITH PARTICULAR REFERENCE TO GASTRECTOMY WITH AND WITHOUT INFRADIAPHRAGMATIC VAGOTOMY\*

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In the early nineteen-twenties Berg (1) (2) and Lewisohn (3) espoused partial gastrectomy as the most satisfactory operation for chronic duodenal ulcer. They were influenced in this decision by the favorable reports from European clinics following this procedure and the proven high incidence of stomal or jejunal ulceration following gastroenterostomy. For many years most surgeons were reluctant to practice gastrectomy for duodenal ulcer, but it is safe to say that at present it is the most widely employed procedure for peptic ulcer.

However, follow-up studies by Mage (4) in our clinic showed that marginal ulceration occurred in about 8 per cent of patients after gastrectomy, although in only about 3 per cent were the symptoms sufficiently severe to warrant further surgery. All of these patients showed abundant free acid on gastric analysis. It is now almost universally agreed that true chronic peptic ulcer does not occur in the absence of free hydrochloric acid.

In an effort to diminish further the hydrochloric acid following gastrectomy, particularly in patients in whom test meals disclosed a high preoperative acidity Klein suggested to Berg that gastrectomy be combined with division of the left vagus nerve. In 1929 Klein (5) published the results in 8 such cases, all of which showed an achlorhydria after six months. In 1934 Winkelstein and Berg (6) extended these preliminary observations after combining gastrectomy with left anterior subphrenic vagotomy in 34 cases. In the light of our present knowledge it is questionable whether these favorable results were more than coincidental but much credit should be given these workers for appreciating and attempting to eliminate the neurogenic factor in gastric secretion. Winkelstein (7) noted an increased night secretion with continuous high acid content in patients with ulcer, a circumstance that could only be reconciled with a continuous secretory mechanism mediated by the vagus nerves.

In 1943 Dragstedt (8) emphasized anew the importance of vagus mediation in producing excessively large amounts of continuous gastric secretion with high acid values in duodenal ulcer, and reported excellent results following complete division of the vagi above the diaphragm.

The operation of choice in this clinic remains partial gastrectomy. It has proven to date to be an eminently satisfactory operation for ulcer even though gastrojejunal ulcer is still a complication occurring mainly in patients who still secrete abundant quantities of free hydrochloric acid postoperatively. These recurrences are more frequent in young males who evidence high preoperative acid values and in patients who have bled repeatedly or who previously had a free perforation. It is in these categories that we prefer, if possible, to add infradi-

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aphragmatic vagotomy to gastrectomy. During the years 1946, 1947 and 1948 an effort has been made to evaluate the relative merits of gastrectomy with and without vagotomy. Observations have been made with particular reference to mortality, morbidity, early and late clinical symptomatology and changes in gastric secretion. Limited follow-up observations have been secured.

#### MATERIAL

This group of cases comprises all patients operated upon for chronic duodenal ulcer on the "C" Surgical Service and the private service of the senior author during the years 1946, 1947 and 1948 upon whom there was performed either subtotal gastrectomy (100 cases) or subtotal gastrectomy combined with infradiaphragmatic vagotomy (84 cases). This group presented the accepted indications for surgery. Intractable pain, unrelieved by repeated courses of medical treatment often under hospital management, formed the largest indication for operation. In this group economic reasons were also a determining factor, for many of these patients, the sole support of a family, could ill afford the many periodic work stoppages that were necessary. Previous alarming hemorrhage or repeated episodes of bleeding (68 cases) comprised another appreciable category. Gastric resection was done in 37 such cases and gastric resection with vagotomy in 31. In 12 of these patients, bleeding was the sole symptom, and whereas we now uniformly combine vagotomy with gastrectomy in this type of case it was not done routinely (7 cases). Experience has shown the marked tendency of hemorrhage to recur in patients without pain, and it is hoped that the addition of routine vagotomy will lessen the tendency to recurrent bleeding. None of these patients were operated upon during the acute episode of bleeding. The problem of management in acute massive hemorrhage of duodenal ulcer origin is still a matter of extreme divergence of opinion. We have been rather conservative in our therapy. Patients have been treated medically and after a period of adequate convalescence, they were operated upon. In a few instances in which bleeding was of a mild nature, operation was done during the same period of hospitalization.

There were 20 patients in whom recurrent symptoms followed a previous perforation. In 8 of these vagotomy was added to resection. Intractable pyloric obstruction which did not respond to medical therapy was another indication for operation in several instances.

The average age of patients upon whom gastrectomy was performed as the sole procedure was 49 years, as opposed to the somewhat lesser age of 42 in the gastrectomy-vagotomy group.

No effort is made to imply that all patients operated upon for ulcer were routinely treated by gastrectomy. In 1944 Colp (9) *et al.* recounting their experiences with gastrectomy stated that approximately 20 per cent of patients were deemed unsuitable for gastric resection. In these a gastroenterostomy was done. Since then an infradiaphragmatic vagotomy has been added in those cases in which it is felt that the surgical risk is not appreciably increased. This group includes patients usually over 60 years of age with a long period of ulcer disease complicated

by obstruction and derangement in electrolyte balance. Included in this group also are cases with cardiorenal vascular disease, diabetes, chronic pulmonary states such as bronchiectasis, symptomatic chronic bronchitis and emphysema. Marked obesity has constituted another deterrent. The technical difficulties in the presence of marked obesity are greatly enhanced. There are no absolute criteria in arriving at a decision as to whether a patient should have a gastrectomy or gastroenterostomy; this is a matter of clinical judgment which must be individualized. A lean, wiry individual of seventy in good condition with a readily movable duodenum may prove a better risk for gastrectomy than a very obese, short, plethoric one many years younger. We have not hesitated to act accordingly and have performed gastrectomy in the former as opposed to the latter.

The local condition at the time of operation was rarely a deterring factor to resection. There were 2 patients in whom preoperative X-rays demonstrated a choledocho-duodenal fistula, barium outlining the extrahepatic duct system. In both the common bile duct was first identified and intubated, and the ulcer excised. We have never found the depth of the ulcer to require identification and intubation of the common bile duct. If a posterior wall ulcer is located so deep as to theoretically require this technical maneuver (10) a postpyloric resection is easily performed. Actual involvement of the common duct occurs more frequently when the ulcer is situated on the anterosuperior wall of the duodenum, infiltrating the gastrohepatic ligament, although even here very rarely. The inflammatory reaction in this location may be excessive obscuring the vital anatomical landmarks. In three cases cholecystectomy was necessitated by an anterior wall ulcer penetrating the adherent gall bladder. The capsule of the spleen was torn in one patient requiring splenectomy. Although preliminary and complementary jejunostomy (11) was formerly frequently used in the obstructed patient to correct the accompanying chemical imbalance, recently improved parenteral means of combating fluid electrolyte and protein deficiencies made jejunostomy necessary in only one patient in this group.

There were no deaths in this series of patients. This reduction in mortality in a period of approximately 10 years has been noted by most large surgical clinics. It reflects the clinical application of increased knowledge in ante-operative preparation particularly in supplying the depleted patient with parenteral fluids in the proper combinations and amounts. The use of blood before, during, and after operation in quantities large enough to maintain normal blood volume has resulted in diminishing operative shock with its profound systemic and metabolic disturbances. This complication nevertheless ensued in mild form in two patients in the gastrectomy group and in one of the gastrectomy-vagotomy series. Refinements in anesthesia techniques, particularly the use of the intratracheal tube and curare have aided the surgeon and patient alike in providing a relaxed and still abdomen in which the technical maneuvers can be carried out expeditiously. The role of the antibiotics is difficult to assay, but it is evident that they have diminished the incidence and lessened the severity of postoperative pulmonary complications which contributed heavily to the mortality before their use. Prompt use of bronchoscopy in the presence of atelectasis has been another aid



in reducing morbidity and mortality. Early ambulation has been practiced routinely, and its many advantages are well recognized.

#### TECHNIQUE

With minor exceptions the technique of gastrectomy that is now employed for duodenal ulcer does not differ materially from that described by Berg (1). As much of the lesser curvature and body of the stomach is resected as is compatible with the anatomical conditions in the individual patient. A relatively small segment of stomach removed from one patient may represent in terms of the remaining portion a wider removal than a much larger portion of a stomach that is markedly dilated and hypertrophied. The visualization of the main branch of the left gastric artery as it emerges from the celiac axis after penetrating the gastrohepatic ligament serves as a reliable guide to the extent of lesser curvature removal. Division of the descending branch at this level insures that no more than about an inch or two of the lesser curvature remains at the completion of the operation as has been repeatedly verified after vagotomy when it is always possible to visualize the esophago-cardial junction. The use of the DePetz clamp further insures resection at the predetermined height. The left gastroepiploic vessel is ligated just below the inferior margin of the spleen. Roughly two-thirds to three-quarters of the stomach is routinely removed. We have never subscribed to the proposal that the extent of resection for gastric ulcer determined the uniformly satisfactory results in this condition, as compared to duodenal ulcer.

The management of the duodenal lesion itself is a phase of gastric resection that has evoked much diversity of opinion. Some surgeons have expressed the viewpoint that for gastrectomy to exercise its greatest benefits the ulcer must be excised. Much depends upon what excision of an ulcer connotes to anyone who has dealt extensively with all the different types of ulcer one is called upon to manage. By definition an ulcer has involved all the layers of the duodenum if it is adherent to a neighboring viscus or anatomical structure (viz., gall bladder, gastrohepatic ligament, pancreas, very rarely the colon). The ulcer base is composed of granulation tissue with a surrounding dense reactive inflammatory process which nature has benevolently provided. To attempt this excision of this barrier, particularly in posterior wall ulcers penetrating into the capsule of the pancreas or anterior superior wall lesions in close proximity to the common duct, is needlessly hazardous. Injury to the pancreas with extravasation of activated proteolytic ferments is one of the prime factors in the initiation of pancreatitis and disruption of the duodenal closure. The safety of gastric resection resides almost entirely on a durable duodenal suture. An ulcer whose base is permitted to rest *in situ* against the pancreas or gastrohepatic ligament so that the mobilized anterior duodenal wall can be sewn safely either to the mucosa below the ulcer or to the thickened pancreatic capsule represents ulcer excision for all practical purposes even though the resected specimen does not show a penetrating lesion with completely encircling mucosa. We doubt very much if all the claims for complete ulcer excision would stand up against critical pathological examination.

Ulcers are not always active at operation. Scarring and fibrosis is both a clinical and pathological entity. Marked stenosis of the duodenum (hour-glass contraction) is the end result. Anterior wall ulcers are so situated that complete excision is readily practised. In the very deeply located duodenal ulcer, usually attended with a great deal of pain, effective closure of the duodenum can be carried out proximal to the lesion (postpyloric exclusion). It is confidently felt that this does not detract from the virtues of the operation provided that the pylorus is completely excised. Guinzburg and Mage (12) showed conclusively that gastroenterostomy healed the duodenal lesion and in the recurrences reported by Mage (4) none were ascribable to the duodenal stump. The prepyloric exclusion operation (Finsterer) as well as the two-stage operation of McKittrick (13) is predicated on the complete subsidence of activity in the excluded duodenum. The operation suggested by McKittrick has the virtue of excising the excluded antrum and pylorus secondarily.

With these criteria it is felt that a pathological report of fibrosis, edge of ulcer or ulcer satisfied every tenet of proper ulcer management and in 164 of the 184 patients the pathological findings were in one of these categories. In 20 specimens no ulcer was found. In 5 of these a deep ulcer was found in the second portion of the duodenum, which the operator knowingly left in situ. In the other 15 cases the presence of scarring, duodenal deformity and thickening justified the operator in feeling that he was dealing with a healed lesion. In only one specimen was duodenal mucosa missing and in this case it had not been the intention to perform a prepyloric "auschaltung".

Gastrointestinal continuity was restored by a Hofmeister antecolic isoperistaltic type of gastrojejunostomy, i.e., applying the afferent loop to the greater curvature of the stomach with the efferent loop consequently in contact with the lesser. All the theroretical arguments for the post-colic anastomosis which has as its bastion the necessity of using a short afferent loop are recognized. Actually as short an afferent loop is employed in performing an anterior anastomosis as can be used retrocolically. There is no evidence clinically that recurrences are higher in one as opposed to the other type of anastomosis. The greater ease of performance of the anterior type of anastomosis without the necessity of having to close the mesocolon about the loops, which after extensive resection may be technically difficult, further enhance its value. Postoperative gastric stasis in the absence of extragastric factors even when vagotomy has been added no longer poses a problem. In this series no patient required re-operation for gastric stasis. The occurrence of "vicious cycle", prolonged gastric retention which not infrequently necessitated re-operation with performance of an entero-anastomosis is still a vivid memory. The diminished likelihood of the development of gastrojejunocolic fistula following an anterior anastomosis and the ease of management should a recurrent ulcer develop are additional reasons for its employment.

When the inflammatory reaction around the ulcer is excessive, the tissues friable and edematous or the security of the duodenal suture leaves any doubt in the mind of the operator, drainage is added. The drain which is sutured to the duodenum to prevent displacement is brought out through a small subcostal

stab wound. There were seven instances of duodenal dehiscence, a complication which in the absence of drainage is frequently fatal, but in this series it was devoid of mortality. This attests to the wisdom of this precautionary measure.

Vagotomy is performed by exerting traction on the gastric stump exposing the diaphragmatic-peritoneal membrane. It is only very occasionally necessary to divide the left coronary ligament of the liver to obtain exposure. It is important that the peritoneum be incised just below where the diaphragm and peritoneum join and directly over the esophagus, otherwise troublesome bleeding will ensue from veins which course across the diaphragm and from the phrenic arteries on either side. Bleeding obscures the operative field and makes recognition of the smaller left anterior nerve additionally difficult. The anterior surface of the esophagus is further exposed by wiping away the fascia adherent to it. At this point the anterior vagus can usually be seen. It is intimately adherent to the esophagus and is separated by finger dissection when it can be recognized by its cord-like feel. It is grasped and dissected upwards into the posterior mediastinum where lateral branches are occasionally encountered, before the main branch is cut and excised. The esophagus is not dislocated until the anterior branch is divided because if the esophagus is made taut the anterior nerve is more difficult to recognize because of its intimate relationship to the esophageal wall. With a finger introduced around the esophagus the larger posterior nerve is usually readily located in the surrounding cellular tissue and hooked around the finger either to the left or right and excised. Whereas in about 80 per cent of individuals the anatomic distribution of the vagus nerves is typical, in the remainder numerous branches that fail to form common trunks have been found to occur in cadaver dissections. This may explain the inability to identify the anterior division of the nerve in four patients. In one case the posterior nerve could not be found. In one instance the esophagus was entered, but this was recognized and sutured without incident.

#### POSTOPERATIVE COMPLICATIONS (TABLE I)

These will be discussed with a view to determine whether the addition of vagotomy results in a disproportionate degree of morbidity, disturbed gastric function or introduces other by-effects in this almost parallel group of cases.

Despite early ambulation which has been used to the fullest, and other ancillary preventative measures pulmonary complications still occur frequently. These were more frequent and severe in the vagotomy series, which is to be anticipated. The manipulations in close proximity of the diaphragm tends to initiate basilar atelectasis. The severity of the pulmonary process is graded up to four. In the gastrectomy group there were a total of 12 instances of pulmonary infection, mild in 8 (Grade I); 4 (Grade II). In the vagotomy group there were 22 pulmonary processes; 9 (Grade I); 10 (Grade II); one (Grade III) and 2 (Grade IV). It is readily appreciated that both in frequency and degree of severity addition of vagotomy predisposes to a heightened incidence of postoperative pulmonary complications. Yet none of these pulmonary infections resulted in a fatality, and the febrile state was only prolonged 2.5 days on the average longer in the vagotomy group as opposed to the gastrectomy group.

The side effects of vagotomy on the functional physiology of the gastrointestinal tract are of particular importance. Attention has been focussed primarily on disturbed motor function of the gastric remnant, small bowel, and large intestine. Postoperative gastric retention and vomiting, also graded according to the degree of severity was sufficiently marked to merit attention in seven instances in the gastrectomy series. Three of these were Grade I; two Grade II, and two Grade III. As was to be anticipated the number with gastric retention in the vagotomy series was slightly higher. Nine patients had Grade I retention, while one was classified as Grade III. In no case was the complication sufficient to prolong the hospital stay unduly and no patient required re-operation for its correction. This experience coincides with all the clinical evidence at hand, that vagotomy plus a drainage procedure, eliminates the deleterious hypomotility with resultant gastric stasis, foul belching, upper abdominal fullness and distress.

Other gastrointestinal postoperative symptoms worthy of note were diarrhea of minor degree in 5 patients in the gastrectomy group. One of these was ascribed to jejunostomy alimentation whereas in the vagotomized group 8 patients divided equally between Grades I and II suffered from this disturbance. A salmonella infection was considered responsible for a severe diarrhea in one of the vagotomy group. Distention was difficult to evaluate etiologically because other factors may have played an extraneous role. In the gastrectomy group one such instance was ascribed to jejunostomy feedings and two to incidental mechanical small bowel obstruction whereas in the vagotomy series all 4 patients with distention of sufficient severity to note this complication presented evidence of an associated peritonitis. In none of these instances was it necessary to use the cholinergic drugs (urecholine or doryl) to combat post vagotomy gastric atony.

Substernal pain and dysphagia were noted more frequently in the vagotomized group. In the latter it occurred 9 times in contradistinction to twice in the non-vagotomized patients. Dysphagia with roentgenologic evidence of achalasia has been reported by other observers following vagotomy. This symptom is usually of short duration. It must be borne in mind that dysphagia occurred in the absence of vagotomy and may be ascribed to the indwelling Levin tube.

Table I lists the major postoperative complications in the two groups of cases.

It will be noted that intra-abdominal suppuration still constitutes both numerically and in terms of severity the most serious postoperative complication of gastrectomy. In this category duodenal dehiscence occurred 7 times; intra-abdominal abscess formation 7 times; peritonitis other than local 5 times. There is no ready explanation for the greater incidence of these occurring in the vagotomized group other than that vagotomy was added in the more severe instances of duodenal ulceration with attendant difficulties and hazards in ulcer excision and subsequent duodenal closure.

Phlebothrombosis of sufficient severity to warrant the clinical diagnosis occurred 6 times; 5 times in the vagotomized group in contradistinction to a solitary instance for gastrectomy alone. No explanation for this variance is at hand. The patients in the vagotomized group were younger, were ambulated as quickly and as efficiently as were those without vagotomy. Venous ligation was not done in any of these cases and pulmonary infarction was not recognized clinically in



any of them. Anticoagulant therapy (heparin and dicoumarol) was the sole therapeutic agent employed.

TABLE I  
*Postoperative Complications*

	GASTRECTOMY	GASTRECTOMY AND INFRA-DIAPHRAGMATIC VAGOTOMY
Pulmonary	8 (mild) 4 (moderate)	9 (mild) 10 (moderate) 3 (severe)
Vomiting and retention	3 (mild) 2 (moderate) 2 (severe)	9 (moderate) 1 (severe)
Diarrhea	5 (mild—one due to jejunostomy feedings)	4 (mild) 4 (moderate) 1 (severe—due to a salmonella infection)
Distention	1 (mild—jejunostomy feedings) 2 (moderate—intestinal obstruction)	4 (severe—with evidence of peritonitis—three with duodenal leaks)
Substernal pain	1 (mild)	1 (mild) 1 (severe)
Dysphagia	1 (mild)	4 (mild) 1 (moderate) 2 (severe)
Duodenal Fistula	2	5
Peritonitis	1	4
Evisceration	1	0
Intestinal Obstruction	1	0
Biliary Fistula	1	0
Phlebothrombosis	1	5
Subhepatic abscess	1	6
Jaundice	0	3

The other postoperative complications were such as might occur after any laparotomy, and were not present in sufficient numbers to be significant. Other than the one case in which the esophagus was entered in performing vagotomy no complications solely ascribable to vagotomy occurred. The so-called vago-

vagal reflex with sudden cessation of cardiac action was not encountered. One patient during the performance of vagotomy had a sudden increase in pulse rate and drop in blood pressure, but moderate shock also occurred in the gastrectomy group of patients.

As accurately as it was possible to judge, morbidity was deemed minimal in 92 of the 100 gastrectomy cases; in 59 of the 84 in which vagotomy was added. Moderate morbidity occurred in 21 cases of the vagotomized group as opposed to only 6, and was severe in 4 of the vagotomized patients in contrast to two in which gastrectomy was practised as the sole procedure.

In summary it would seem that certain postoperative complications were more numerous and severe in those cases in which vagotomy was added to gastrectomy. The disturbed gastrointestinal physiology was of short duration and did not continue in excess of three months, and will be discussed in more detail

TABLE II  
*Early Postoperative Symptoms (up to Three Months)*

	GASTRECTOMY	GASTRECTOMY WITH INFRA-DIAPHRAGMATIC VAGOTOMY
Vomiting	3 (mild)	6 (mild) 2 (moderate—one with foul belching)
Diarrhea	2 (mild) 1 (moderate)	6 (mild) 2 (moderate)
Pain	5 (mild) 3 (severe—2 of these patients had proven jejunal ulcers)	7 (mild) None severe
Bleeding	2 (severe—jejunal ulcers)	None severe
Dumping Syndrome	2 (mild) 1 (moderate)	2 (mild) 1 (moderate)

in evaluating the results of operation in both groups of patients. The absence of mortality in both groups emphasizes that vagotomy can be added to gastrectomy without jeopardy.

#### FOLLOW-UP

These results will be discussed from the clinical and physiological points of view. The follow-up ranged from 4 to 42 months. The duration of the data includes those obtained from the study of 89 of the 100 patients in the gastrectomy series, and 79 of the 84 in whom vagotomy was added. It was of interest to evaluate the early postoperative symptoms of which patients complained in these comparable groups, and a period of 3 months was selected for this purpose (table II). With minor exceptions these symptoms disappear with reassurance, dieto-therapy and medical management.

Although symptoms attributable to motility disturbances were much more

frequent in the vagotomy group, they did not begin to approach the frequency, severity, or duration of those which have been found to occur when vagotomy is done as a *sole* procedure. Mild vomiting occurred 3 times in the gastrectomy group. In the vagotomy cases it was minimal in 6 patients and moderate in 2, one of whom suffered from foul eructations. Diarrhea occurred 3 times in the gastrectomy group, and 8 times in the vagotomy cases. No patient required re-hospitalization because of these complaints nor were they very disabling. A mild

TABLE III  
*Late Postoperative Symptoms (4 to 42 Months after Operation)*

	GASTRECTOMY 89 OF 100 PATIENTS	GASTRECTOMY WITH INFRA-DIAPHRAGMATIC VAGOTOMY 79 OF 84 PATIENTS
Pain	4 (mild) 2 (moderate)  2 (severe—jejunal ulcers)	3 (mild) 2 (moderate—due to gall bladder disease)
Vomiting	1 (mild)	1 (mild)
Diarrhea	2 (mild)	7 (mild—1 due to milk intolerance) 2 (moderate)
Bleeding	2 (severe—jejunal ulceration)	None
Dumping syndrome	3 (mild)	2 (mild)
Dysphagia	None	1 (mild)
Summary		
Well	79	69
Well with minor symptoms	7	9
Jejunal ulcers	3	0
Death (Homologous serum jaundice—inter-current)		1

dumping syndrome, i.e., a train of symptoms initiated by the ingestion of food, characterized outstandingly by dizziness, sweating, palpitation, tachycardia and weakness, occurred 6 times equally divided among the groups.

Mild pain was experienced by 5 patients in the gastrectomy and 7 in the vagotomy group. Severe pain, however, was found only in the gastrectomy group in 3 patients, 2 of whom suffered from jejunal ulceration and one from cholecystitis. Bleeding was only encountered in the gastrectomy group. It was seen in 2

patients, one of whom also had pain. There were, therefore, 3 recurrent jejunal ulcers, which occurred within the first 3 months after discharge from the hospital.

In the later periods of observation many of these early symptoms became milder or disappeared, except among the 3 recurrent ulcers. Non-ulcer type of pain occurred about equally in the 2 groups. Occasional vomiting was experienced by one patient in each group. Diarrhea continued to be more frequent in the vagotomy group, and all but one ceased to have pain on swallowing.

In summary, 79 of the gastrectomized cases were considered well; 69 of the combined group were judged to have had an excellent result. Sixteen patients, 8 in each series, were well with minor symptoms. Three patients with gastrectomy alone had proven jejunal ulcers. None in the vagotomized series had a known recurrence. One patient died months after operation of an homologous serum jaundice.

Cognizance is taken of the hazards of analyzing this material on anything other than a temporary basis in the knowledge that the ulcer diathesis is not basically remedied by surgery. Trends in recurrences have been evaluated in

TABLE IV  
*Postoperative Secretion Studies*

TEST	GASTRECTOMY		GASTRECTOMY WITH INFRA-DIAPHRAGMATIC VAGOTOMY	
	No. Cases	Anacid	No. Cases	Anacid
Gruel (early).....	31	14	29	29
Gruel (late).....	20	16	15	15
Night (early).....	9	7	29	28
Histamine (early)....	24	8	54	36
Histamine (late)....	21	11	34	30

large groups of cases showing that by and large the early postoperative years yield the largest number of operative failures. The recurrences in this group of patients have been early, supporting this contention. We feel it is of some significance that up until now no recurrent ulcer has been verified, where vagotomy and gastrectomy were combined.

#### TEST-MEAL STUDIES (TABLE IV)

Gastrectomy was primarily advocated to diminish the chemical or hormonal phase of gastric secretion. Theoretically eliminating the psychic or cerebral component should further complete a reduction in acid secretion. Irrespective of any underlying etiological factor in ulcer production long clinical experience has verified the fact that free hydrochloric acid apparently is a *sine qua non* in chronic peptic ulceration. Complete achlorhydria following gastrectomy for chronic peptic ulcer of the stomach in contradistinction to the ability of the gastric remnant to secrete acid in cases of duodenal ulceration, has proven the factor in uniformly obtaining cures in the former as opposed to occasional recurrences in the latter.



Postoperative gastric secretory studies following gastrectomy for duodenal ulcer have shown reduction or elimination of acid in only about one-half the cases. Studies both, early and late, of the secretory activity of the stomach following gastrectomy and vagotomy were done to determine the effect of these combined procedures on acid production.

Test meals were performed in the early and late postoperative periods using gruel, night secretory studies and histamine in combination or singly as opportunity presented itself. Of 31 patients tested with gruel in the gastrectomy series 14 proved anacid to this stimulus. All 29 patients tested were anacid in the gastrectomy-vagotomy group. Late gruel studies (3 months or longer postoperatively) revealed 15 of the 15 tested in the vagotomy group anacid, whereas of the 20 tested in the gastrectomy group only 16 were anacid. Night secretory tests showed 7 of 9 anacid in the gastrectomy cases whereas 28 of the 29 tested showed no free acid in the vagotomy group. Histamine is recognized as the most powerful gastric acid stimulant for clinical purposes. Test meals carried out using this drug early in the postoperative period disclosed only 8 achlorhydrias among 24 patients in the gastrectomy group, whereas 36 of 54 patients in the vagotomy group were anacid. In the late tests the superiority of the combined procedure in the production of achlorhydria were even more strikingly demonstrated. In the gastrectomy group 11 of 21 patients tested or 52 per cent were anacid. In the vagotomy group 30 of 34 patients or 88 per cent were anacid.

The insulin test as advocated by Hollander (14) to detect the presence of intact vagal fibers after vagotomy was performed on 41 patients during the early postoperative period. Five were positive indicating incomplete section of the nerves.

The occasional incomplete vagotomy as determined by the insulin test is attributable to the many anatomical variations in the vagus nerve. However, from our experience with vagotomy there would seem to be no definite correlation between the completeness of vagotomy and its clinical effects (15).

#### SUMMARY AND CONCLUSIONS

The reduction of gastric acidity is an aim of both medical and surgical therapy for peptic ulcer. To prevent recurrent ulceration the goal of surgery should be an achlorhydria. Whereas subtotal gastrectomy accomplishes this in a certain number of instances, experience in 84 cases of subtotal gastrectomy combined with bilateral infradiaphragmatic vagotomy reveals much more frequent achlorhydria in this group as opposed to subtotal gastrectomy alone. The relatively slight increase in morbidity when vagotomy is added further recommends this procedure in young individuals with high preoperative acid values. Follow-up studies, even though of short duration, reveal no recurrences among the 84 cases so treated in contradistinction to three proven recurrences in 100 patients with gastrectomy alone. A longer period of observation will be required definitively to assay the merit of vagotomy with gastrectomy but at this time it would seem as though this combined procedure had very definite value.

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## PRESERVATION OF THE PYLORIC ANTRUM IN RESECTION OF HIGH GASTRIC LESIONS

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In the presence of either a high penetrating ulcer of the cardia or of carcinoma involving the oral half of the stomach resection which will preserve the pyloric antrum is to be recommended under specific conditions.

An ulcer of the cardia demands a very high transection of the fundus, if extensive inflammatory involvement of both walls of the stomach is present or if malignant degeneration is suspected. In such cases a resection done according to Billroth's second procedure, with removal of body, antrum and pylorus, will have a functional result just as though a total gastrectomy, had been done.

It will be recalled that in Billroth's second procedure the digestive tract is reconstituted by means of anastomosis between the small residual portion of the fundus and the jejunum. Nourishment is very rapidly evacuated by such a "stomach", and the digestive action of the subnormal amount of gastric juice is minimal.

The other clinical condition which without necessity is apt to induce the surgeon to sacrifice the pyloric antrum is carcinoma involving the oral half of the stomach. Cancer originating in the fundus frequently remains silent, and is unsuspected for a considerable space of time, due to the absence of clinical symptoms and x-ray evidence, until finally the lesion has progressed to involvement of the cardiac stoma. The area of malignancy will then be so extensive that excision of at least the entire upper half of the stomach down to the junction of fundus and antrum must be done.

Total gastrectomy has come to be generally regarded as the operation of choice in fundus carcinoma. In fact, Leahy has recently supported the point of view that total gastrectomy be done for gastric malignancy regardless of location or degree of involvement. However, a certain percentage of totally gastrectomized patients die of malnutrition after a postoperative interval of weeks or months, despite the most careful dietetic supervision. Moreover, it is well known that the danger of recurrence in residual gastric tissue after subtotal gastrectomy is negligible, in contrast to the frequency of distant metastases.

The rationale of the procedure here endorsed is based upon the fact that the preservation of the antrum in these cases will insure, to a varying degree, against postoperative gastric invalidism. Although the pyloric antrum produces only a small amount of hydrochloric acid and pepsin, its secretin-effect will induce maximal secretion from the minute portion of a residual fundus.

This method of gastric resection for certain lesions of the upper part of the stomach, is by no means a new procedure. In fact, the era of radical surgery in the treatment of gastric ulcer was initiated by the so-called sleeve resection as recommended by Payr in 1909 and v. Redwitz in 1918. But the late results of Payr's operation were quite unsatisfactory, especially because a considerable percentage of patients submitted to the sleeve resection acquired recurrent ulcers

usually at the line of resection. Even the immediate postoperative course was often stormy because of gastric retention of varying degree and duration, and without an obvious organic basis. Today, with the accumulated experience in gastric surgery satisfactory explanations for the pitfalls of Payr's operation are apparent. The recurrent ulcers were due to the inadequate extent of the resection of the body and fundus of the stomach. The Payr resection was limited to the narrow part of the stomach which harbored the ulcer.

The secondary gastric retention can also be accounted for by the fact that in transecting the stomach, all vagus fibers are necessarily severed; and—as in bilateral vagotomy more or less, pylorospasm of various duration is bound to follow.

The error of a too limited resection of body and fundus is avoided by an extensive sleeve resection recommended by us. *But be it noted that it is done for ulcer patients, only if the remnant of fundus is minimal*, and in cancer cases, as above mentioned, when the fundus and body are completely excised.

Pylorospasm can be eliminated, if a pyloromyotomy (of the Fredet-Rammstedt type) is to be done.

The advocated procedure avoids the development of the "dumping stomach"; this definite advantage may be said to parallel the advantage secured by improved secretory function. Wangenstein considered the "dumping stomach" to be a major untoward consequence of the Billroth II resection and has lately been doing an extensive sleeve resection even in duodenal ulcers so as to obviate rapid evacuation. In his cases he added an open pylorotomy (of the Finney type) to counteract the resulting pylorospasm.

There are, however, frequently cited objections to the practicability of an end-to-end anastomosis, objections which have been repeatedly made ever since the gastroduodenal anastomosis in the Billroth I type of resection was first performed. Most surgeons prefer avoiding an anastomosis which must overcome the difficulty of uniting lumina of greatly different size. Moreover, the point has been stressed that extensive gastric resection (as in ulcer patients) cannot avoid excessive tension.

These misgivings have probably prevented the general application of an end-to-end anastomosis of fundus and antrum or esophagus and antrum respectively, in spite of the functional advantages of these procedures.

The various arguments against an end-to-end anastomosis have been disproved particularly by von Haberer, who modified the technic of the Billroth I procedure, thirty years ago. As to the extent of resection, we believe that with adequate mobilization of the duodenum, approximation of the stumps without undue tension is possible in every case, including the various types of sleeve resection discussed above.

The following technical points may be worth recording from the surgical point of view:

Satisfactory approach to the cardiac part of stomach and lower esophagus can be obtained by the following incisions (fig. 1):

1. Left paramedian and supra umbilical transverse incision.



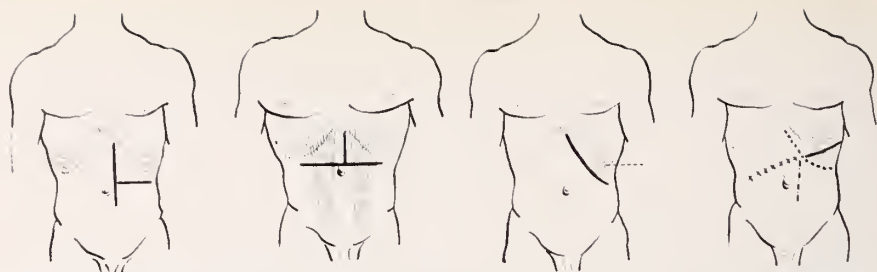


FIG. 1. Incisions for exposure of cardiac part of stomach: 1. Left paramedian plus left transverse incision (incision of choice in acute costal angle); 2. Supraumbilical transverse plus left paramedian incision (incision of choice in obtuse costal angle); 3. Left subcostal incision for mobilization of the costal arch; 4. Several variations of the abdomino-thoracic incision.



FIG. 2. Marwedel's mobilization of left costal arch. Transection of costal cartilages indicated by dotted line.

2. Large transverse incision, dividing both recti muscles, and left paramedian incision.
3. Left subcostal incision and mobilization of the costal arch.
4. Combined abdomino-thoracic incision.

While all these incisions give adequate access to the left subphrenic space, the necessary exposure of the lower end of the esophagus depends on local conditions which cannot be predicted before the operation.

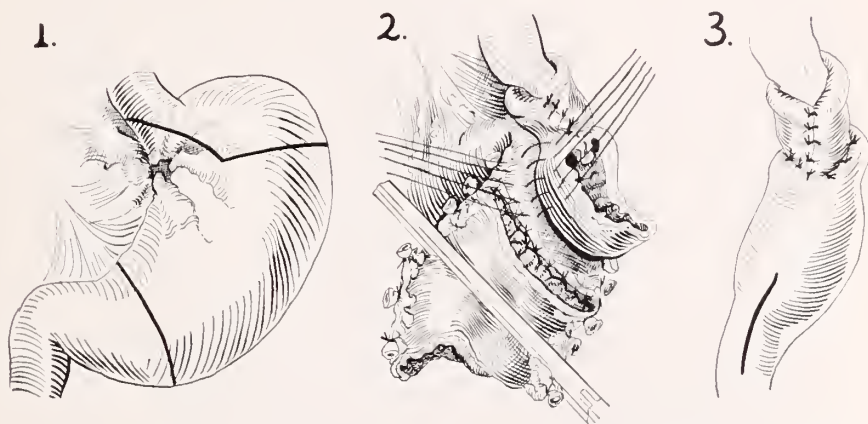


FIG. 3. Technique of resection in large penetrating juxta-esophageal ulcer: 1. Lines of transection. 2. The small remaining part of the fundus is wrapped around the end of the esophagus. The posterior wall of fundus and antrum at the site of the future end-to-end anastomosis are brought together by seromuscular sutures of silk, which are not tied. The posterior wall of the antrum is incised down to the submucous layer, bringing into view the submucous vessels. These are ligated by means of suture ligatures placed with big bites in order to diminish the circumference of the lumen of the pyloric antrum. 3. Anastomosis terminated, pyloromyotomy performed.

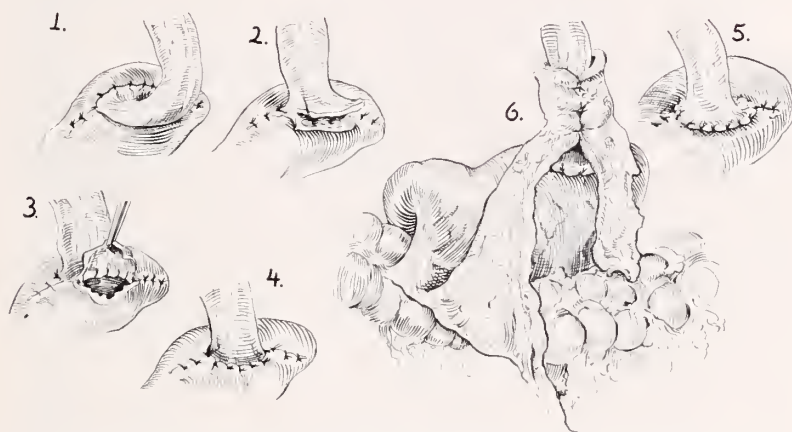


FIG. 4. Technique of end-to-end anastomosis of lower end of esophagus and pyloric antrum following resection of the upper half of the stomach.

If the cardiac end of the esophagus can be sufficiently mobilized from below and pulled down into the abdominal cavity for 8–10 cm., the abdominal approach is sufficient. In patients with an acute costal angle we prefer a longitudinal incision, in patients with an obtuse costal angle a transverse incision.

A subcostal incision, combined with transection of the cartilaginous part of

the costal arch as advised many years ago by Marwedel, gives also excellent exposure (fig. 2).



FIG. 5. Large penetrating ulcer of the gastric cardia before and after sleeve resection. Arrows indicate ulcer crater and pylorus, respectively.

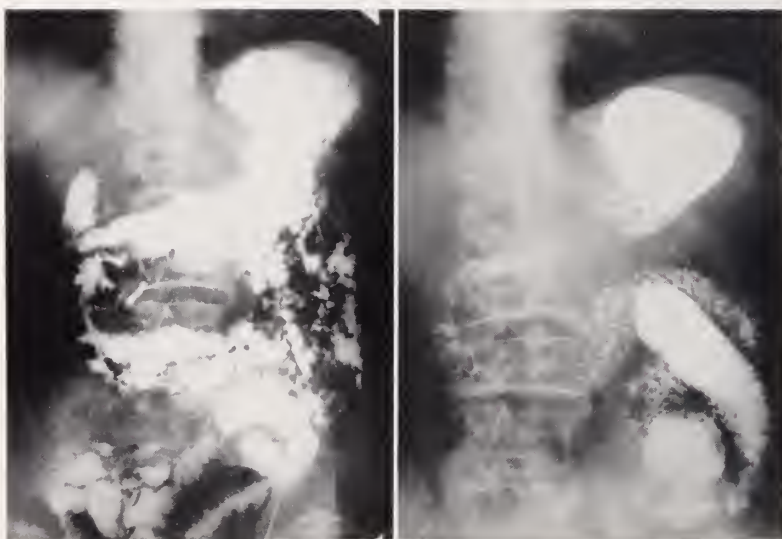


FIG. 6. Penetrating ulcer of the gastric cardia, before and after sleeve resection

But, in many penetrating juxta-esophageal ulcers and in large carcinomata of the upper end of the stomach involvement of either the left lobe of the liver, diaphragmatic hiatus, or cardiac end of the esophagus do not permit proper mobilization of the lower esophagus from below. Then the combined abdomino-thoracic approach is indicated. Kirschner's fish hook incision (1926), a para-



FIG. 7. Penetrating ulcer of the gastric cardia, before and after sleeve resection



FIG. 8

FIG. 8, 9, 10. Roentgenograms in a different patient, on whom resection of cardia, fundus and body of stomach and end-to-end anastomosis of esophagus and pyloric antrum was performed (for carcinoma).



median incision extended into the 8th intercostal space (Garlock) or an oblique incision which runs in the direction of the long axis of the stomach serve equally well for this purpose (fig. 3).

As to the technique of the anastomosis the inequality of the lumina of the residual fundus and antrum can readily be corrected by shortening the diameter of the antral stump with the help of submucous suture ligatures as recommended



FIG. 9



FIG. 10

by von Haberer in the Billroth I operation. These have the added advantage of securing perfect hemostasis. In excision of the upper half of the stomach the esophago-antrum anastomosis can be performed by the end-to-end or end-to-side method. Several different implantations of the esophagus stump have been recommended to preclude possible stenosis. Our technic pictured in Figure 4 is similar to the one which has been successful in ureter-bladder anastomosis.

Mobilization of the duodenum and pyloromyotomy, both integral parts of the operation, are performed as advised by Kocher and Fredet-Rammstedt respectively. X-ray pictures illustrating the postoperative result are shown in Figures 5, 6, 7 and 8, 9, 10.

#### SUMMARY

In certain cases of penetrating ulcer of the cardiac part of the stomach and of cancer of the oral half of the stomach preservation of the pyloric antrum is advised. The foodway is reestablished by fundus-antrum and esophagus-antrum anastomosis respectively.

Indications for this type of resection and the essential details of its technic are discussed.

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## PUDENDAL HERNIA

### REPORT OF A CASE OPERATED UPON BY THE ABDOMINAL ROUTE

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Because of the rarity of pudendal hernia, the paucity of reported cases, and the failure of operative measures for its relief in the past, it was deemed advisable to record an instance of this unusual form of hernia which apparently has been successfully repaired. To date, there have been only fifteen cases of this condition reported in the literature. Operative procedures have been undertaken on seven of these patients and in only four of these has cure been accomplished.

Pudendal hernia was first described by Mery in 1739, in the "Transactions of the Royal Academy of Sciences of Paris". However, it was Sir Astley Cooper in 1807 who gave the first detailed report of such a case. A brief summary of the previously reported cases follows:

*Case 1.* Reported by Mery. A female, 6 months pregnant presented herself with an egg-sized hernia, which was easily reducible, and the contents of which were obviously bladder.

*Case 2.* Reported by Curade. A 26-year old female, 6 months pregnant presented a lateral perineal tumor which increased in size on standing. On compression of the tumor, urine was expressed.

*Case 3.* Reported by Cooper. A 22-year old female presented a hernia the size of a pigeon egg. Inspection revealed a swelling below the middle of the left labium, while the upper portion of the labium, and the inguinal ring were free. On palpation, the tumor extended up alongside the vagina, and gave an impulse on coughing. The hernia was retained with a T-binder.

*Case 4.* Reported by Cooper. A female, who presented a swelling similar to, but smaller than the previous one, and situated in the right labium. It transmitted an impulse on coughing, appeared while standing, and disappeared in the recumbent position.

*Case 5.* Reported by Cloquet. A 24-year old female presented a chestnut sized hernia in the posterior right labium, which was reducible.

*Case 6.* Reported by Hartmann. On post-mortem examination, a tumor of the labium was discovered, which was found to consist of prolapsed bladder.

*Case 7.* Reported by Hager. A 28-year old female, during her first confinement presented a walnut-sized swelling in the right labium. The swelling increased in size over a four year period, at which time, during her second confinement, it was found to be the size of a pigeon's egg.

*Case 8.* Reported by Koenig. A case presenting a pudendal hernia the sized of a man's hand was seen, but no further details were given.

*Case 9.* Reported by Von Winckel. A female, who had had several difficult deliveries presented a right labial swelling. A pessary, and truss were used to no avail. A plastic operation per vagina was attempted, but was unsuccessful.

*Case 10.* Reported by Von Winckel. A 51-year old female, had noted right

labial swelling at the age of 46. Treatment with a truss resulted in failure. At laparotomy loops of intestine were found adherent to the sac, which could not be liberated. Ventral fixation of the uterus was performed, with subsequent recurrence of the hernia. A second operation was performed from below. The sac was opened, the contents reduced, and the sac obliterated by suture. Following this procedure, a small hernia recurred.

*Case 11.* Reported by Moschowitz. A 41-year old female, who had been delivered by forceps, noted a mass protruding from the vagina. Numerous operations were performed, including several vaginal plastic procedures, without success. Following second pregnancy, the condition became unbearable, and abdominal exploration was attempted. Bladder and small intestine were found in the sac, and a cystopexy was performed, following which the hernia recurred. A second abdominal exploration was performed, which revealed a sliding hernia consisting of bladder. The hernial ring was bounded by the ascending ramus of the pubis externally, and by the soft tissues of the bladder mesially. The uterus was dislocated, and used to plug the hernial ring, but was followed by a recurrence within one year.

*Case 12.* Reported by Grattan. A 53-year old female presented a mass, the size of a hen's egg in the left labium. On abdominal exploration, using a suprapubic incision, a loop of sigmoid was found descending through an opening in the pelvic floor. The internal ring of the hernia was bounded anteriorly by the posterior reflexion of the left uterosacral ligament, and postero-laterally by the rectum. The rectosigmoid was fixed, and the sigmoid appeared to slide down along the posterior surface of the broad ligament into the hernial ring. A protrusion occurred through a rent in the levator ani muscle, and passed through a triangle bounded externally by the ischiocavernosis, internally by the constrictor cunni, and posteriorly by the transversus perinei. The sigmoid was reduced, and the ring closed without attempt to extirpate the sac. The sigmoid was anchored to the left psoas at the brim of the pelvis, and again two inches above that.

*Case 13.* Reported by Chase. Twenty-one months prior to admission, when the patient was four months pregnant, she noted the onset of sharp pain in the right lower quadrant, vagina and rectum, followed by vomiting, constipation, and distention. Bulging of the vagina was noted at this time. The vaginal mass interfered with and made delivery difficult. The hernia enlarged after delivery and presented itself in the posterior portion of the right labium and was the size of an adult fist. It was easily reducible, and on straining, the entire vagina was occupied by a soft mass which descended on the right parallel to the vagina. It was bounded by the vagina medially and by the descending ramus of the ischium laterally. A two-stage operation was performed following a dilatation and curettage for therapeutic abortion. Through a suprapubic incision, a loop of sigmoid was found knuckled through a hiatus bounded by the right sacro-uterine ligament mesially, and the base of the right broad ligament. Bladder was found in the sac and was withdrawn. The sac could not be inverted even after pushing from below by an assistant. The peritoneal margins of the ring were therefore incised,



and the rectovesical fascia was closed. The peritoneum was closed over this. The broad ligament was next imbricated over the sacro-uterine ligament to close the fossa. The sigmoidal loop was withdrawn from the pelvis and a sigmoidopexy was performed. In a second stage, an incision was made in the right labium, and the subpubic triangle was exposed, bounded internally by the constrictor cumi, externally by the ischiocavernosus and below by the right transversus perinei muscle. The sac was found adherent to the levator fibers and was freed to its neck, split, and transfixed. The torn levator was sutured and a levator myorrhaphy was performed. The torn and attenuated ischiorectal fascia was repaired.

*Case 14.* Reported by Marble. A female presented a hernia in the left perineal region between vagina and rectum. Two abdominal repairs were unsuccessful. A third repair was attempted, using a two-stage operation. The first stage consisted of an abdominal approach, with reduction of the contents of the sac, and closure of the defect of the perineal floor. The second stage consisted of a perineal approach, with removal of the hernial sac. A myxomatous tumor was found, originating in the left broad ligament, and perforating the levator ani muscle.

*Case 15.* Reported by Yeomans. A case is reported, in which an abdominal approach alone was utilized, and with an assistant giving counter pressure through the perineum, the sac was inverted. A purse-string suture was placed above its apex, and the sac was obliterated using three other similar sutures.

#### DEFINITION AND CLASSIFICATION

A pudendal hernia is a hernia located in the pudendum, its essential anatomical feature being a defect in the levator ani muscle and its fascia, which form the internal ring of the hernia. The hernia may originate anterior or posterior to the broad ligament, and descends to the pudendal region where it is bounded by a triangular space consisting of the ischiocavernosus muscle laterally, the bulbocavernosus medially, and the transversus perinei posteriorly (figs. 1 and 2). This latter muscle is an important landmark in differentiating a pudendal from a perineal hernia, which is the more common of the two. The perineal hernia presents in the ischiorectal fossa, posterior to the transversus perinei muscle.

An excellent classification of pudendal hernia has been suggested by Chase, based upon the anatomy of the structures involved, and in which he substitutes the term levator hernia for pudendal.

Levator hernia:

1. Congenital
  - (a) Anterior to the broad ligament
  - (b) Posterior to the broad ligament
  - (c) Combined (anterior and posterior)
2. Acquired
  - (a) Anterior to the broad ligament
  - (b) Posterior to the broad ligament
  - (c) Combined (anterior and posterior)

## REPORT OF CASE

This was the fourth M. S. H. admission of a 46 year old white female housewife, complaining of a swelling on the left side of the perineum of one year's duration. Over the 19 years prior to the present admission, the patient had submitted to 14 different gynecologic procedures, and had had three pregnancies, terminated by normal "easy" deliveries, though forceps were used in all three. For the sake of completeness, the previous operations are listed below:

1930: Excision of right ovary and appendix, and myomectomy. Cholecystectomy was performed 10 days later for cholelithiasis.

1935: Spontaneous abortion followed by D. & C.

1940: Vaginal approach for excision of a cervical cyst.

1940: Excision of a left ovarian cyst.

1941: Vaginal hysterectomy.

1941: Vaginal plastic.

1942: Repair of cystocele on three (3) different occasions.

1947: Insertion of a tantalum plate for urethrocele and cystocele, followed by two revisions for covering of the urethral plate.

1949: First attempt at repair of the pudendal hernia from below, which failed.

One month after the second revision of the tantalum plate, in December, 1948, the patient noted a swelling to the left of the fourchette, extending to the left labium posteriorly. The swelling was associated with severe pain in the region of the fourchette, radiating to the left buttock. It was not associated with urinary or bowel symptoms. The swelling enlarged on standing, walking, and straining, and disappeared on reclining, with attendant relief of pain. In July, 1949, an attempt was made to repair this hernia at another institution, but the surgeon terminated the operation when he encountered bowel. Symptoms have continued unabated since.

Her past history is fully given in the preceding list of previous operations.

*Examination:* The patient, an obese white female in no acute distress, was negative on general examination. Her blood pressure was systolic 130 and diastolic 68. The abdomen revealed healed surgical scars in the right upper and lower quadrants.

*Vaginal examination:* Marital introitus, the tantalum plate was felt along the anterior vaginal wall. There was a globular, walnut sized swelling to the left of the posterior portion of the left vulva, extending into the vulva, anterior to the anus, and anteromedial to the ischial tuberosity. The mass appeared after standing and walking, was easily reducible, presented an impulse on coughing, and disappeared in the reclining position. Rectal examination was negative.

*Laboratory findings:* Urine, acid; Specific Gravity, 1.020; albumin 0, sugar 0; white blood cells 2-3; epithelial cells, few. Hemoglobin was 15.4 Gm.; white blood cells, 8,900; seg, 62; nonsig, 10; lymphocytes, 19; monocytes, 7; eosinophiles, 1; plasma cells, 1.

*Operative procedure:* (J. H. G.): A left lower rectus muscle splitting incision was made. Many pelvic adhesions were present, and it was necessary to free these as well as the rectum and adnexae before the defect in the pelvic floor could be visualized. The rectum was found prolapsed through an opening in the pelvic floor, medial to the descending ramus of the left pubis, and through the fibers of the levator ani muscle. The rectum was carefully mobilized, and freed from the hernial ring. It was apparently bound down to the split levator fibers by scar tissue resulting from the previous perineal surgery. The ring was closed with three interrupted sutures of black silk through the levator ani muscle, and rectovesical fascia. The rectum was mobilized by incising its peritoneal reflection, and bluntly dissecting it free from the sacrum. The rectum was pulled upwards, and maintained in that position, by suturing it to the presacral fascia with several interrupted silk sutures. The operative area was reperitonealized with fine chromicized catgut and the peritoneum at the internal ring of the hernia was closed with interrupted black silk. The abdominal wound was closed with

interrupted figure of 8 #30 steel wire and clips. The patient was given 500 cc. of whole blood during the operative procedure, which was performed in the Trendelenburg position.

The *post-operative course* was uneventful. The patient was kept in bed until the eighth post-operative day, when progressive ambulation was instituted. She was discharged on the fifteenth post-operative day, at which time examination revealed no recurrence of the hernia, with firm closure of the ring.

#### DISCUSSION

*Etiology:* The most important single causative factor in producing a pudendal hernia seems to be pregnancy and subsequent parturition. All reported cases have emphasized this feature. Trauma during childbirth has been noted repeatedly. In our case, there remained, in spite of normal childbirth, a residual

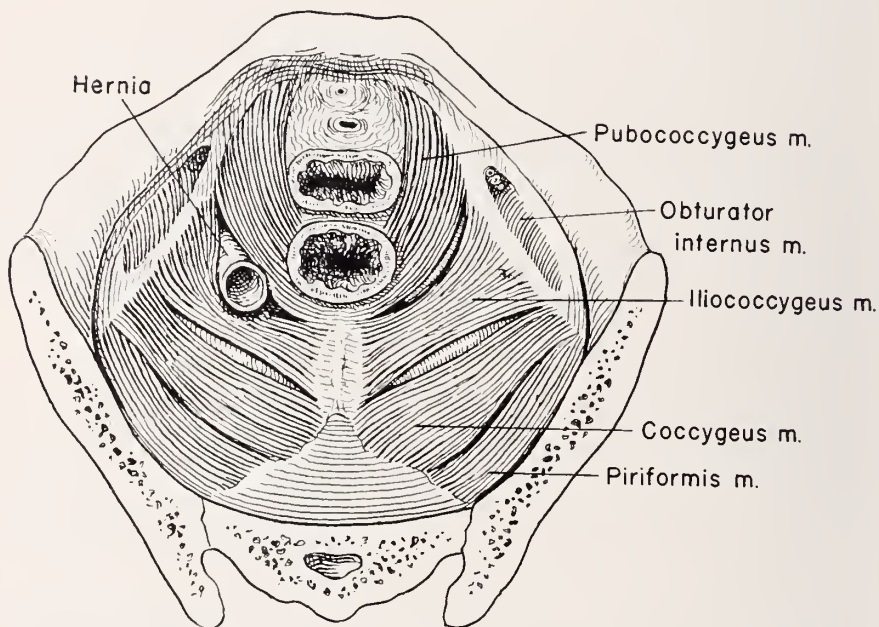


FIG. 1. The pelvic diaphragm from above, showing the exit of the hernial sac

cystocele and urethrocele, which required many operations until correction was consummated. All verified reported cases were in females of the child-bearing age, ranging from 21 to 51 years of age. In addition, the general factors pertaining to the etiology of hernia in general must be remembered.

*Surgical Anatomy:* Point of Entrance (or internal ring): This may be anterior or posterior to the broad ligament, thus giving rise to three varieties of pudendal hernia, namely, anterior or direct, posterior or indirect, and lastly, a combined type, in which the sac originates behind the broad ligament, and pushes forward beneath it, to break through the levator anteriorly.

Anatomically, the levator consists of two portions, the iliococcygeus, and the pubococcygeus. Medially, these two muscles fuse with the pubococcygeal and rectococcygeal raphe. However, laterally, the iliococcygeus does not overlap or

fuse with the pubococcygeus, thus leaving a potential defect on each side, which is situated immediately behind the broad ligament. In this region, the rectovesical fascia is separated from the ischiorectal fascia only by areolar tissue (fig. 1). Anterior to the broad ligament, this potential defect in the pelvic diaphragm does not exist, since the iliococcygeus and pubococcygeus overlap and fuse with each other. This anatomical finding explains the predominance of posterior hernias, and also the fact that the anterior variety is almost always associated with direct pelvic trauma related to childbirth. The boundaries of the internal ring in the posterior variety form a triangle, the two arms of which

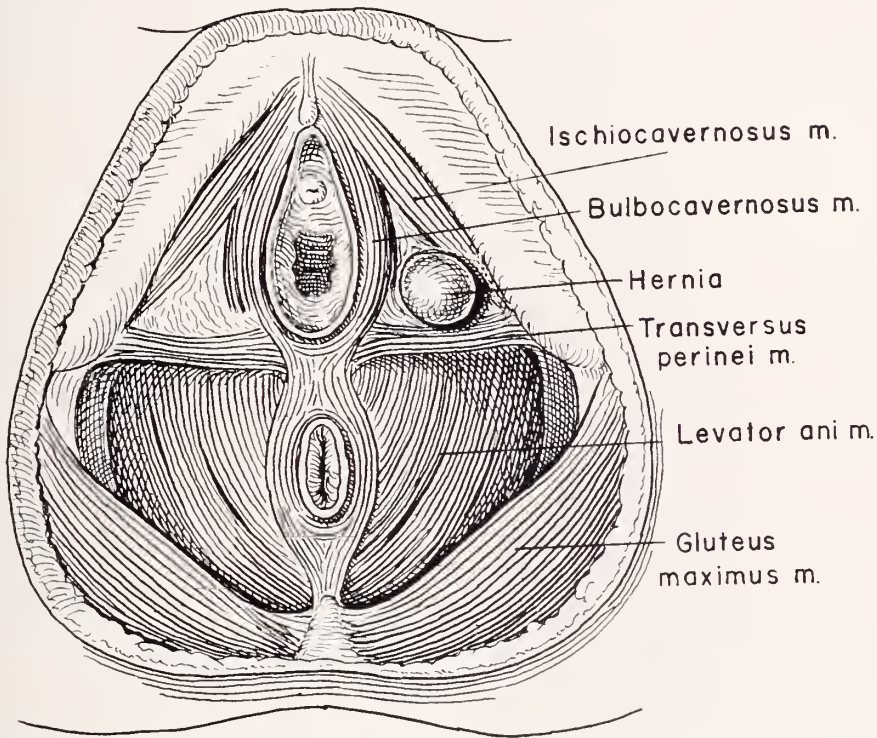


FIG. 2. The subpubic triangle and its boundaries, showing the emergence of the hernia sac in its characteristic site.

are the broad ligament anteriorly, and the sacro-uterine ligament and rectum medially. The anterior variety is bounded by the uterus and bladder medially, and the round ligament laterally.

The external ring (fig. 2) of a pudendal hernia is a triangular area, bounded by the bulbo-cavernosus muscle medially, the ischio-cavernosus muscle laterally, and the base of the triangle is formed by the transversus perinei muscle. This latter muscle is significant in the differentiation between pudendal and perineal herniae.

The course of a pudendal hernia is downward and forward. It perforates the rectovesical fascia, and extends to the ischiorectal fascia, to make its exit in the



previously described triangle. In passing from the rectovesical to the ischiorectal fascia, the hernia may pass through the potential weak spot of the pelvic diaphragm previously described, or it may perforate the levator. It may also perforate the rectovesical fascia, and burrow beneath the broad ligament before perforating the levator. This latter type forms the basis of the combined type of hernia.

The rectosigmoid is the only fixed portion of the sigmoid loop. The long sigmoidal loop doubles up, or knuckles itself at this point, and burrows forward along the posterior aspect of the broad ligament, just at the weak spot in the pelvic diaphragm. This portion of the pelvic diaphragm is penetrated by the sigmoidal loop of bowel, thus forming a sliding hernia of the sigmoid. The anterior variety, due to the fact that a defect exists in the pelvic diaphragm anterior to the broad ligament, always contains bladder, and thus forms a sliding hernia of the bladder.

*Diagnosis:* The essential features in the diagnosis of a pudendal hernia are:

1. Signs of hernia, e.g. impulse on coughing, enlargement of the mass in the upright position and on walking, and ability to reduce the mass which may be spontaneous on change of position.
2. The hernia appears in the subpubic triangle, anterior to the transversus perinei muscle, and is usually found in the posterior portion of the labium major. Thus the medial aspect of the hernia is covered by vaginal mucosa, and the lateral aspect by skin.

*Treatment:* In this type of hernia, as in others, excision of the sac should, if possible, be carried out. The abdominal approach is preferable since it is easier to reduce and determine the contents of the sac. It is important to suture the rent in the pelvic diaphragm, as well as to repair the rectovesical fascia. In the posterior variety, the sigmoid colon is invariably present as a sliding hernia. It is therefore important to mobilize the sigmoid and rectosigmoid, and reduce the kinked portion of bowel. Following mobilization of the bowel, a sigmoidopexy is performed, fixing the sigmoid and rectosigmoid to the presacral and iliopsoas fascia. This combination of mobilization of the rectosigmoid and sigmoidopexy, with firm closure of the pelvic diaphragm and internal ring, performed through an abdominal incision, should result in a cure of the hernia. Some surgeons have deemed a second perineal stage advisable, when the sac is extirpated from below, and the pelvic diaphragm is firmly sutured, after which a levator myorrhaphy is performed, suturing the levator muscles together in the median line.

#### SUMMARY AND CONCLUSIONS

1. All reported cases of pudendal hernia have been briefly reviewed.
2. A case, apparently successfully repaired, has been presented.
3. The etiology, surgical anatomy and treatment have been discussed in detail.

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## THE RESULTS OF SPHINCTEROTOMY IN PANCREATITIS\*

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There is a widely held belief that pancreatitis is due to reflux of bile into the pancreas, since surgical decompression of the biliary tract is the usual treatment both for acute pancreatitis and for the severe, painful, chronic condition. Although we consider that decompression is useless and dangerous during the acute phase, and of temporary value for chronic pancreatitis, we do agree with the theory that reflux of bile into the pancreas is the etiological factor in the majority of cases (1, 2, 3).

Reflux of bile under tension into the pancreas can occur only if two conditions are present:

1. *A common passageway.* This means that the bile duct and the duct of Wirsung join above the papilla of Vater, and do not have separate entrances into the duodenum (fig. 1).

2. *Spasm of the sphincter of Oddi.* Occlusion of the papilla, either temporarily as a result of spasm of the sphincter of Oddi, or more rarely, by a small calculus, must be present if reflux is to occur. It follows, therefore, that if the sphincter of Oddi is sectioned, reflux under tension should no longer occur.

We have studied 52 cases of pancreatitis to determine whether a common passageway was present in these patients and to find out whether section of the sphincter would prevent further symptoms. The diagnosis in these patients was made on the history and physical findings. There was confirmation in 24 cases by the finding of a high serum amylase during an acute attack. In 22 other patients the pancreas was found to be hard and fibrosed at operation. In the remaining 6 patients the diagnosis could not be confirmed either by a high serum amylase or by evidence of fibrosis of the pancreas when examined at operation. In 2 of the patients who had a high serum amylase while under observation, the pancreas felt normal to palpation at subsequent operation. The secretin test showed diminished pancreatic function in 23 of 44 patients in whom it was performed. The gallbladder had been previously removed in 16 of the patients and was found to be diseased or to contain stones in 12 cases. In 20 patients the gallbladder was found to be thin-walled and normal although frequently it was surrounded by dense adhesions. In 4 cases common duct stones were found. Calcification of the pancreas as evidenced by x-ray examination was found in 4 patients.

The operative procedure was always carried out when the acute symptoms had subsided and after X-ray examination of the gallbladder, stomach and duodenum were completed. Whenever possible the secretin test was done (4). At operation, following cholangiographic studies, the sphincter of Oddi was sectioned either through the common duct by a special instrument (5, 1) or

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transduodenally by making a small incision in the anterior duodenal wall. In 29 patients sphincterotomy was carried out endocholedochally and in 23 patients transduodenally. In sectioning the sphincter care was taken not to injure the duodenal wall, since the oblique passage of the common duct through the wall prevents duodenal reflux after sphincterotomy. The gallbladder was removed whenever it was present whether it was normal or diseased. In patients who were to be studied post-operatively a T-tube was implanted in the common duct. Following operation cholangiographic and reflux studies were made before

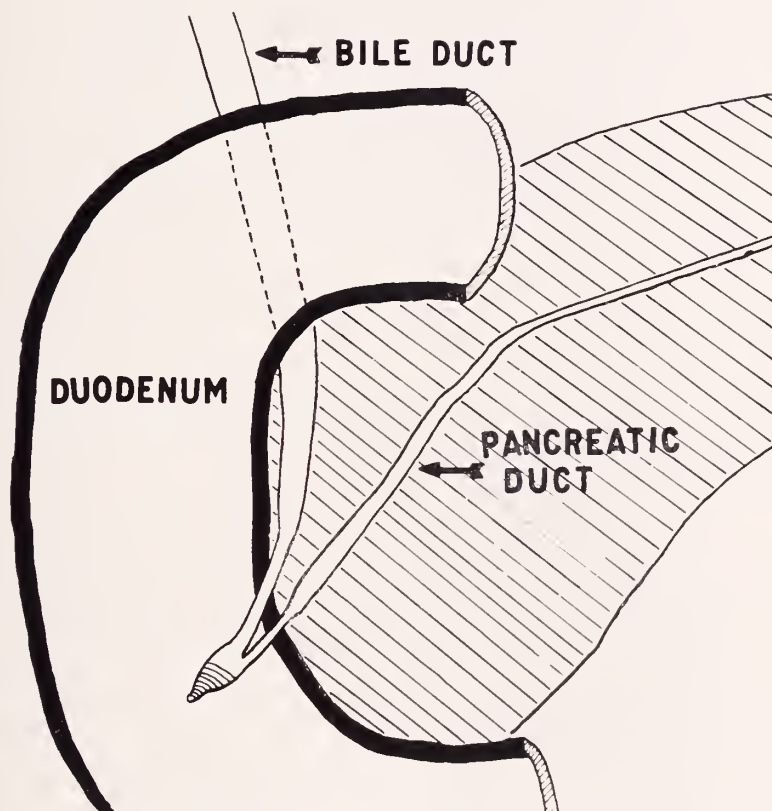


FIG. 1. Diagram illustrating the common passageway. The bile and pancreatic ducts join above the papilla of Vater so that obstruction at that point by spasm or stone enables bile to pass into the pancreatic duct or pancreatic juice to flow up the biliary tract.

removal of the tube. In a small number of patients the common duct was closed and a small drain placed down to it.

A common passageway was demonstrated by the following means:

1. *Operative cholangiographic studies.* Diodrast was injected either through the cystic duct or through the common bile duct while the sphincter of Oddi was rendered spastic by the application of hydrochloric acid through a Rehfus tube (fig. 2).

2. *By direct inspection at operation.* In patients in whom the sphincter was





FIG. 2. Operative cholangiogram in a case of pancreatitis. Spasm of the sphincter of Oddi was produced deliberately by the introduction of N/10 hydrochloric acid into the duodenum through a Rehbus tube. Injection of diodrast through the cystic duct not only visualized the biliary tract but also the whole length of the pancreatic duct

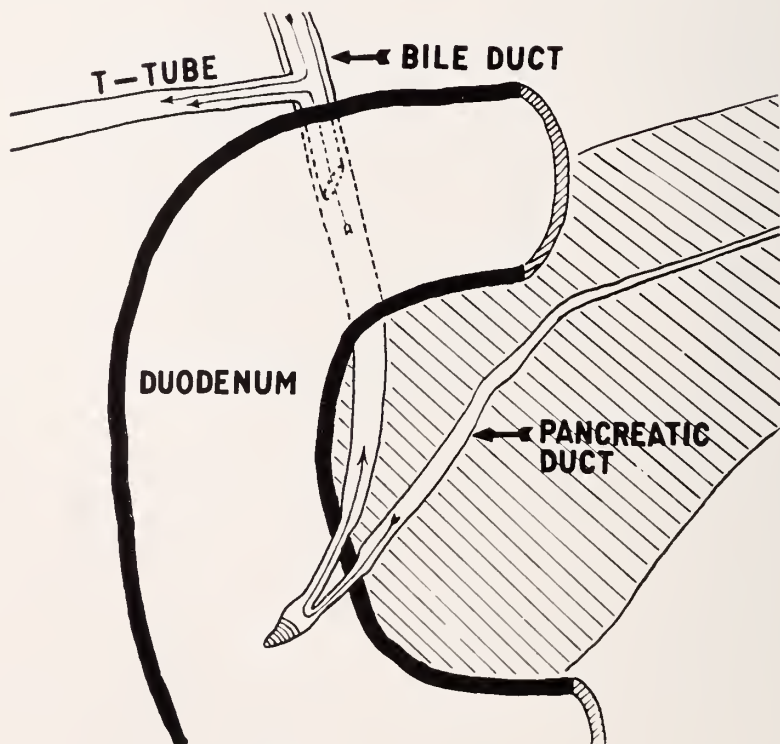


FIG. 3. Reflux of pancreatic juice produced deliberately. In a patient with a T-tube in the common bile duct the intraductal pressure is low. The flow of pancreatic juice under stimulation of secretin will be diverted in part up the common bile duct and mix with the bile. Analysis of this bile for amylase will indicate the degree of reflux of pancreatic juice.

sectioned transduodenally, the opening of the pancreatic duct into the ampulla could be demonstrated by injecting secretin intravenously. The ensuing flow of pancreatic juice visualized the orifice of the pancreatic duct.

3. *By reflux studies post-operatively.* In patients with a T-tube in the common duct, the injection of secretin resulted in a profuse flow of pancreatic juice, some of which passed up the common bile duct and was detected in the biliary drainage by analysing it for amylase (fig. 3). In the absence of a common passageway this reflux did not occur (4, 6).

The findings are summarized in Table 1. It will be noted that in 49 of the 52 cases, one or several of these observations could be carried out. In 48 of the 49 patients who were operated on for pancreatitis, a common passageway was demonstrated.

TABLE 1  
*Demonstration of a common passageway*  
52 Cases of Pancreatitis

By Cholangiogram .....	13
By Cholangiogram and reflux .....	17
By Cholangiogram, reflux and direct inspection .....	9
By Cholangiogram and inspection .....	1
Inspection and reflux .....	4
Reflux.....	2
Absence of common passageway (cholangiogram only).....	1
No opportunity for any observation.....	3

TABLE 2  
*Results of Sphincterotomy*  
52 Cases of Pancreatitis

Good (loss of symptoms and gain in weight).....	42
Poor (persistence of gastro-intestinal symptoms; no pancreatitis) .....	3
Failures (severe chronic alcoholics).....	2
Post-operative deaths.....	3
Died of Carcinoma of Pancreas—8 months post-operative .....	1
Not followed .....	1

The results of the operations are presented as a preliminary report since the follow-up period varies only between 3 months and 3 years. 42 of the patients are well in that they have no further attacks of pain and they have gained from 10 to 60 pounds in weight. In 3 patients the results are considered poor since they continue to complain of pain in various parts of the gastro-intestinal tract although as far as can be determined, they have no more attacks of pancreatitis. Two cases are failures; both are severe chronic alcoholics and have recurrent attacks of pain when they drink a large amount of alcohol. In 1 patient, definite proof of recurrent pancreatitis was found since the serum amylase was elevated on two occasions. The other patient has severe attacks of pain without elevation of serum amylase. One patient could not be traced. Three patients died following operation; one due to a transfusion reaction; another due to a severe

hepatitis with widespread hemorrhage and, the third as a result of injury to the common bile duct. The results are summarized in Table 2.

#### DISCUSSION

The proof of a common passageway in all but 1 patient studied supports the theory that pancreatitis is due to reflux of bile into the duct of Wirsung. The good results following the section of the sphincter of Oddi tend to confirm the correctness of the theory. The failure in two patients following sphincterotomy indicates that in a small proportion of cases alcohol is a factor in the production of pancreatitis. The mechanism of its action is not understood.

Other modes of therapy have been suggested: 1) to destroy the sensory nerves leading from the pancreas by sympathectomy or coeliac ganglionectomy (7-9). This may abolish the pain but does not stop the progress of the disease. It also removes all sensory reflexes that may be produced by other disease of the gastro-intestinal tract. 2) Another method suggested is to relax the sphincter and abolish the nervous phase of secretion of the pancreatic juice by periesophageal vagotomy. Vagotomy should be successful but has the disadvantage of denervating almost the whole gastro-intestinal tract. 3) The third approach is to prevent reflux of bile into the pancreatic duct either by tying off this duct or by tying off the common bile duct and shunting the bile directly into the intestine by a cholecysto- or choledochoduodenostomy or jejunostomy. In the one case the intestine is deprived of pancreatic juice unless the accessory duct is open. In the other case the direct anastomosis of the biliary tract to the intestinal tract is a complicated procedure. It is our opinion that the direct approach by cutting a tiny muscle, the sphincter of Oddi, is both the logical one and the simplest one.

#### SUMMARY

The presence of a common passageway in 48 of 49 cases of pancreatitis that were studied supports the theory that the disease is due in the majority of cases to reflux of bile into the pancreas. The cessation of symptoms following sphincterotomy confirms the opinion that the reflux of bile is due to spasm of the sphincter of Oddi.

The persistence of symptoms in two chronic alcoholics after sphincterotomy suggests that alcohol may be a specific etiological factor in a small proportion of cases.

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## AVULSION OF THE DIAPHRAGM

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Avulsion of the diaphragm resulting in a herniation of the abdominal viscera into the thorax without rupture of the diaphragmatic muscle is a rare condition. Many cases of traumatic rupture and congenital or acquired eventration have been reported. However, cases of avulsion of the diaphragm are extremely rare. In 1927, Bryan reported a case in a man forty years old who was injured in an auto accident. The injury involved the left chest. Immediate dyspnea and nausea were noted. X-rays showed the diaphragm had been torn away from its lateral attachment and the abdominal viscera were protruding into the thoracic cavity. An attempt was made to suture the diaphragm to the chest wall, but the patient did not survive the operation.

In the case to be reported, insertions of the left hemidiaphragm were partially torn away from the ribs, costal cartilages and lumbar spine, causing a huge herniation of the diaphragm into the chest. Contained in the hernia sac was the stomach and transverse colon, a portion of the small intestine and the spleen, forming a voluminous mass which extended upwards into the chest to the level of the seventh rib. In this case, the left hemidiaphragm acted as the wall of a large hernial sac. There was no rupture of diaphragmatic continuity, but the symptoms were those of a diaphragmatic hernia.

### CASE REPORTS

*History.* The patient was a man, aged 31 years, who was first admitted to the Jewish Hospital on the 24th of April, 1948. The chief complaint on admission was upper abdominal pain associated with attacks of severe dyspnea which had been present for a year and a half. The attacks were recurring at increasingly frequent intervals, especially after meals. The pain was so severe that the only real relief was obtained from hypodermics of morphine sulphate. The most recent attack occurred one week prior to admission. The pain of the attacks was not associated with nausea, vomiting, diarrhea or constipation.

The past medical history was generally normal until 1944. At that time, the patient was working for a railroad. He sustained a crushing injury when caught between two cars of a freight train. The right leg was amputated at the thigh and the left leg sustained multiple fractures. Many of the ribs were fractured. The patient was placed in a body cast at this time and shortly thereafter, the attacks of pain which brought the patient to the hospital had their onset.

*Examination* of the chest revealed dullness at the left base. Active peristalsis could be heard over the precordium. The cardiac point of maximum intensity was shifted to the right. The abdomen was generally negative. The right leg had been amputated above the knee. The left leg was partially ankylosed and only about thirty degrees of flexion was possible. The scars of multiple skin grafts were noted. Blood pressure was 154 systolic and 90 diastolic.

Fluoroscopy of the chest revealed the presence of a marked elevation in the left hemidiaphragm. In the recumbent posture, it was elevated to the level of the seventh rib posteriorly. There was accompanying displacement of the heart and mediastinal structures to



the right. The trachea was displaced to the right. Films showed segments of lobular atelectasis involving the midportion of the left lung. Thickened pleura was visualized over the right lower lobe. These changes were apparently post-traumatic in origin. Barium progressed well through the esophagus into the stomach. The stomach lay just beneath the elevated left hemidiaphragm. Study in the lateral plane revealed a sharply demarcated contour of the elevated stomach and left hemidiaphragm with the demarcation in the anterior third of the left hemithorax. This, apparently, represented a post-traumatic deformity of the left diaphragm. In view of the incomplete involvement of the left hemidiaphragm it appeared to present a herniation post-traumatic in character. Fluoroscopic observation revealed restricted mobility of the remaining portion of the left hemidiaphragm.



FIG. 1. Preoperative roentgenogram showing elevation of the lateral portion of the left hemidiaphragm with upward displacement of the stomach.

The stomach, except for its displacement in the cephalad direction, was regular in contour. There was no evidence of peptic ulcer or carcinoma. Progress through the small intestine was unretarded (fig. 1).

*Course.* Following the oral administration of Priodax, there was no visualization of dye in the gallbladder. The patient was advised that a two months therapeutic trial of a fat free diet in conjunction with antispasmodics should be undertaken, and he was discharged.

The patient was readmitted to the hospital on the 20th of May, 1948, complaining of severe pressure in the epigastrium following the ingestion of food. Because of the continuing discomfort, and as a result of the previous studies, it was felt advisable to operate on the patient.

On the 28th of May, 1948, the patient was operated upon under intratracheal cyclopropane and oxygen anesthesia supplemented by intravenous sodium pentothal. An incision was made over the seventh rib and a portion of the sixth, seventh and eighth ribs were excised. It soon became apparent that the entire left half of the diaphragm had been avulsed from its normal attachments, but had become adherent to the lateral chest wall at a higher level. The musculature of the diaphragm appeared normal in thickness. The left lower lobe of the lung had completely collapsed as a result of upward pressure. The dome of the diaphragm occupied the lower half of the left pleural cavity. No effort was made to resuture the diaphragm to its normal attachments. The thoracic wound was continued downward toward the abdomen which was opened. The abdominal contents of the hernial sac were



FIG. 2. Postoperative roentgenogram. The stomach has returned to its normal position and the dome of the diaphragm is no longer elevated.

reduced through this incision. It was then possible to place several plicating sutures of heavy silk in the diaphragmatic muscle. As a result, the upper level of the diaphragm was depressed approximately two interspaces. The left lower lobe was reexpanded by the anesthetist. The thoracic wound was closed and a stab wound was made through which a catheter was inserted for water seal drainage was discontinued after approximately 48 hours. Following this, the chest was aspirated on several occasions.

The patient was readmitted to the hospital on the tenth of July, 1948. He complained of pain in the midsternum and epigastric regions. A draining sinus was present in the otherwise healed thoracic wound. Several heavy black silk sutures were removed through this wound sinus. On X-ray examination, the left hemidiaphragm was found to be obscured.

Adhesions were present between the left lung and the chest wall. The cardiac silhouette appeared enlarged. The trachea and mediastinum were not displaced. The fifth, sixth, seventh and eighth ribs on the left side showed evidence of operative fracture. A catheter inserted into the left lower chest injected with lipiodol showed a fistula in the left thoracic wall. There was no evidence of herniation of the diaphragm and the abdominal contents seem to have been restored to their normal position (fig. 2). After a few days in the hospital, the patient's symptoms were relieved and he was discharged.

Following this admission, the patient was seen at frequent intervals. On several occasions, silk sutures were removed from the draining sinus. With the removal of the last silk suture from the thoracic wound sinus, the wound healed promptly. The patient is now enjoying excellent health. He is able to eat all types of food and the symptoms of gallbladder disease previously noted, have not recurred.

#### SUMMARY

Traumatic rupture of the diaphragm and congenital eventration are relatively common conditions. The case here reported represents a very rare situation, namely, a traumatic avulsion of the diaphragm from its lateral attachments. The symptoms were similar to those of a diaphragmatic hernia. Complete symptomatic relief was obtained by means of a combined abdominothoracic operation which reduced the abdominal contents from the thorax. Plication of the diaphragmatic muscle was used to maintain reduction. No attempt was made to return the lateral attachments of the diaphragm to their normal position. The operation has resulted in complete relief of the disturbing symptoms previously noted.

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# CARCINOMA OF THE GALL BLADDER

## A REPORT OF 32 CASES

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This paper is based on a report of 32 cases of carcinoma of the gall bladder, gathered from the records of the Newark Beth Israel Hospital, covering a period of 13 years between 1936 and 1949 inclusive. During that same period 2360 gall bladder operations were performed at the same hospital. The incidence of carcinoma of the gall bladder in this series was 1.3 per cent. A short review of 26 of these cases was published in 1948 (1). Since that time 6 additional cases were gathered from our hospital records, making a total of 32 cases of primary carcinoma of the gall bladder. There were 29 females or 91 per cent, and 3 males or 9 per cent. Thirty-one of these cases contained stones. In one male patient an inflammatory process of the gall bladder was found, but no stones. Biopsy showed primary carcinoma of that organ. This is the only case of carcinoma of the gall bladder without stones in this series. These operations were performed by 11 different surgeons. Nine operations were performed by 1 surgeon, 8 by another, one did 4. Six operations were equally divided between 3 others, and the remaining 4 surgeons performed 1 operation each.

The number of cases included in this report is rather limited. No attempt is made to form any definite conclusions with reference to the etiology, the incidence or the mode of treatment of this disease from such meager clinical material. However, there are several important points that will bear careful analysis, such as the high incidence of stones in the carcinomatous gall bladder in this group, failure of early recognition, a comparison of the preoperative and postoperative findings, the duration of illness and previous history of jaundice.

Carcinoma of the gall bladder was considered a rather uncommon disease until the last half of the last century. The earliest reports were based on autopsy findings. Abdominal surgery during that era, particularly surgery of the gall bladder was still in a primitive stage. Hence surgeons had very meager opportunities to observe this pathologic condition in the living. The first report of carcinoma of the gall bladder was made by Maximillian Stoll. Two authors give the date as 1771 (2 and 4). Another writer (3) gives the date as 1777. However, the exact date is of very little importance. We gather from the literature that this condition was occasionally recognized at the beginning of the nineteenth century. Clinical observations began to accumulate at the end of that period. At that time attempts were made to formulate a clinical picture of the disease. Surgical treatment did not receive any serious consideration until the end of the last century. From 1870 on the number of reported cases began to increase. Vilard reported 26 cases and made a complete analysis of the number of cases reported up to

\* From the Surgical Services of the Newark Beth Israel Hospital.



that time (4). Musser analyzed 100 cases in 1899, and a similar number of cases were summarized by Courvoisier in 1890. In 1902 W. J. Mayo reported 400 operations on the biliary tract for all causes, with a .5 per cent incidence of carcinoma of that organ. At the beginning of this century many contributions appeared in the surgical literature from many eminent surgeons, both European and American, notably W. J. Mayo, Moynihan, Judd, Deaver, Robson, Rolleston, Illingworth and many others. No attempt will be made in this paper to enter into a collective review of primary carcinoma of the gall bladder, since collective reviews of this disease have appeared from time to time during the last decade. The most recent and comprehensive review of this subject worthy of note appeared in a recent issue of "Cancer" magazine (2).

The attempt to determine the approximate incidence of carcinoma of the gall bladder, derived from the statistics which were gathered from the collective reviews, is still not definite. So far, the exact estimation of the incidence has not been irrefutably established. In the most recent reviews of the subject, statistics

TABLE I

Number of Cases	32
Females	29 or 91 per cent
Males	3 or 9 per cent
Average Age	60
Oldest	79
Youngest	47
Cholecystectomies	17
Cholecystostomies	11
Cholecystectomies and choledochostomies	3
Cholecystectomy and partial Hepatectomy	1

are quoted (2) from 206,098 necropsy records gathered by 23 different authors, showing a total of only 98 cases of primary carcinoma of the gall bladder in that group. This represents an incidence of 0.43 per cent. This is in direct variance with statistics gathered by earlier writers, whose incidence of primary carcinoma of the gall bladder was 4.5 per cent. This extreme variation in the incidence of this disease is probably due to the fact that some of the surgical reports are based on a selected, limited group of cases encountered by individual surgeons. This variation is best illustrated by a report of 25 operations (2) on the gall bladder, in which 4 cases proved to be primary carcinoma of that organ, making an incidence of 16 per cent, as compared with 569 cases of carcinoma out of a total of 46,400 operations on the biliary tract, giving an incidence of 1.2 per cent. It is hoped that as the number of cases reported in the recent literature increases, there will be an opportunity to come closer to an approximate estimation of its true incidence.

*Etiology:* Many observers consider stones as the causative factor in carcinoma of the gall bladder. The frequency with which calculi are found in association

with cancer of the gall bladder, and its experimental production in animals by the insertion of foreign bodies into that organ, lead some writers to accept the theory that stones may be the primary factor in the production of this disease. In a review of 413 cases reported in the American literature by 9 different authors (1), the presence of stones in carcinoma of the gall bladder varied from 60 to 100 per cent. The average incidence was 76 per cent. Only one author in the foreign literature, Janowski (4), reports an incidence of 100 per cent.

Experimental production of carcinoma of the gall bladder in animals by introducing foreign bodies into the gall bladder was attempted by Kazama, Barlowe, Burrows, etc. Petrov and Krotkina (5) attempted to produce experimental carcinoma of the gall bladder in 1928. In 1933 they reported that carcinoma developed in two of the animals. In 1947 they reported another series of experiments in which they tried to prove the relationship of foreign bodies to carcinoma of the gall bladder. One hundred guinea pigs were used in this experiment. Of this number, fifty-one animals survived 14 months or longer. In 5 of these animals, epithelial proliferation of the gall bladder wall, with characteristics of malignant growths was found. These animals survived between 14 and 35 months. Four showed metastasis to distant organs. From these experiments they concluded that, "The development of malignant growths following the introduction of hard foreign bodies into the gall bladder is established." In the guinea pigs, the process requires over a half, and sometimes over two years. Microphotographs to substantiate their conclusions were submitted.

On the other hand, quite a number of capable clinicians and painstaking investigators believe that there is no direct relationship between gall stones and carcinoma of the gall bladder. Harold Burrows placed gall stones and other foreign bodies in the gall bladders of 50 guinea pigs, who were kept alive for over one year before they were sacrificed. Autopsy did not reveal carcinoma in any of their gall bladders. Some are of the opinion that stones which are so frequently found in carcinomatous gall bladders are secondary to that pathologic process, and not the direct cause of it. Other investigators are of the opinion that a combination of other factors in addition to the calculi may determine the formation of carcinoma, such as frequent inflammatory conditions causing cellular hyperplasia, etc.

*Age and Sex:* The age of patients with carcinoma of the gall bladder usually corresponds to the age group of all carcinomas. The most common occurrence is during the sixth decade. In our series of cases, the average age was 60. The oldest was 79, and the youngest was 47. The disease predominates in women in direct relationship in which gall bladder disease in general predominates in the female. In our series the ratio was 9 females to 1 male, or 91 per cent to 9 per cent.

*Clinical Factors:* Unfortunately there is no clear-cut clinical picture suggestive of primary carcinoma of the gall bladder. In a great many cases the history may only reveal a long period of either frequent or occasional attacks of gall bladder colic, with some gastrointestinal disturbance which one usually associates with gall stones. The duration of illness may vary. Very few cases with carcinoma of the gall bladder are diagnosed preoperatively.

## ANALYSIS OF OUR 32 CASES

Of the 32 cases in this group admitted to our hospital for operation, a definite diagnosis of carcinoma of the gall bladder was made on admission in only one case. In two cases, suspicion of carcinoma of the head of the pancreas was entertained by the surgeons referring the patients to the hospital. In other words, in 97 per cent of the cases admitted for observation or operation, the diagnosis of malignancy was not made. In 15 cases, the admission diagnosis was either acute cholecystitis, cholelithiasis or gall bladder disease. Carcinoma of the head of the pancreas was made in two. Hydrops of the gall bladder was made four times; obstructive jaundice was considered in three cases; common duct stone in one; tumor of the colon, in one; diabetic coma associated with gall bladder disease in one. In one case the diagnosis of intestinal obstruction was made. This was a case of intestinal obstruction due to a stone which perforated the gall bladder into the intestine, and at operation a perforated gall bladder with carcinoma was

TABLE II  
*Admission diagnosis*

Cholecystitis, cholelithiasis, gall bladder disease .....	15
Carcinoma of the head of the pancreas.....	2
Hydrops of the gall bladder.....	4
Obstructive jaundice.....	3
Common duct stone.....	1
Tumor of the colon.....	1
Diabetic coma, associated with gall bladder disease.....	1
Intestinal obstruction .....	1
Cardiac asthma, with suspicion of gall bladder disease.....	1
Enlarged gall bladder, with hypertension .....	1
Mononucleosis, suspicion of liver disease.....	1
Cholelithiasis with carcinoma of the gall bladder.....	1
Total .....	32

found. A diagnosis of cardiac asthma with suspicion of gall bladder disease, enlarged gall bladder with hypertension, and mononucleosis with suspicion of liver pathology, were made in three other cases.

*Duration of Illness:* In surveying the case records, we find that in 27 cases, the history of previous duration of illness varied from 21 days to 30 years. The average duration was  $9\frac{1}{2}$  years. In 5 cases no history as to the exact duration of illness was obtainable, either because of the acute emergency situation, or the inability of the patient to give a detailed account of the past illness. Most of these patients gave a history of previous attacks of colicky pain, either of mild or acute nature associated with digestive disturbances. In many of these cases the attacks were of short duration, not requiring medical attention. Histories of the recent illness, which were obtained from 29 patients after they were brought to the hospital, showed an average of 2 months duration.

*Jaundice:* Twenty-six of these patients gave no history of attacks of jaundice

prior to their present illness. Six gave a history of one or more repeated attacks of jaundice transitory in nature, between one month and twenty years previous to their present illness. In this group of jaundiced cases, one gave a history of jaundice 20 years ago; one 18 years; one 11 years; one  $2\frac{1}{2}$  years; one 1 year, and one 1 month. Fourteen of these 32 cases had jaundice of various degrees upon admission to the hospital. In four, the jaundice was very marked. In the remaining it was mild. It is interesting to note that in those who gave a history of previous attacks of jaundice, the duration of the jaundice as elicited from the histories was rather short. In only one was a history of three years duration obtained. In the remaining cases, the average duration was about one month. In four of the cases who gave a history of previous jaundice, perforation of the gall bladder either into the generalized peritoneal cavity, or into the contiguous viscus was found at operation.

*Roentgenography:* Fifteen of the 32 cases were submitted to roentgenographical examinations at the hospital preparatory to operation. Among the remaining number of patients who were admitted to the hospital with a diagnosis of gall bladder disease, some had gall bladder visualizations performed by their private physicians before they were referred to the hospital. A few of the cases were of an emergency nature, where the element of time did not permit roentgenographical studies. This is the reason why in only approximately 45 per cent of the patients cholecystography was done in the hospital. However, in not one of the 15 cases in which gall bladder visualization was done, was the diagnosis of carcinoma of the gall bladder made preoperatively. The most common x-ray interpretation in these 15 cases was "Pathological gall bladder". A reference to stones was made in only one case. The high percentage of failure to visualize stones in these cases is rather unusual when compared with the high percentage of positive findings in the cases of cholelithiasis not complicated with malignancy.

*Blood Studies:* Twenty-three cases showed an average red cell count of a little over 4,000,000 and a hemoglobin of 79.7 per cent. In several of these cases, the blood studies were repeated, yielding the same average. It is interesting to note that in spite of the variability of the dissemination of the malignant process, there was little alteration in the hematological picture. With the exception of two cases of advanced infiltrating neoplasm, both erythrocyte and hemoglobin levels were maintained at a fairly normal concentration.

*Preoperative Diagnosis:* It is interesting to note that even in those cases who remained in the hospital for several days being prepared for operation, which included intravenous medication, blood studies, x-ray examination, examination of stools and urine, etc., only two cases were diagnosed as definite carcinoma of the gall bladder preoperatively. Two were diagnosed as possible carcinoma of the pancreas. The diagnosis of intestinal obstruction was made in one case and corroborated at operation. The obstruction was due to an old spontaneous cholecystoduodenostomy, with the expulsion of three stones into the intestinal tract, causing the obstruction. A diagnosis of appendicitis, which was made in one case was justified, because of a gall bladder perforation which evidently occurred 24 hours previous to the patient's admission to the hospital. At operation



a perforation of a carcinomatous gall bladder with extensive peritonitis was found.

TABLE III  
*Preoperative diagnosis*

Cholelithiasis and carcinoma of the gall bladder.....	2
Possible carcinoma of the pancreas.....	2
Cholecystitis, cholelithiasis, hydrops of gall bladder.....	11
Common duct stone.....	1
Acute cholecystitis.....	4
Empyema of the gall bladder.....	3
Enlarged liver.....	1
Intestinal obstruction.....	1
Gall bladder disease.....	4
Obstructive jaundice.....	2
Acute appendicitis.....	1
Total.....	32

TABLE IV  
*Diagnosis at operation*

Cholecystectomy operations	
Carcinoma of the gall bladder.....	7
Cholecystitis and cholelithiasis.....	5
Empyema of the gall bladder.....	4
Ruptured gall bladder with perforation into duodenum, intestinal obstruction.....	1
Total.....	17
Cholecystectomy and choledochostomy	
Adenocarcinoma of the gall bladder.....	1
Carcinoma of the gall bladder and cholelithiasis.....	1
Cholecystitis, hydrops of gall bladder.....	1
Total.....	3
Cholecystectomy and partial hepatectomy	
Carcinoma of the gall bladder.....	1
Cholecystostomy operations	
Carcinoma of the gall bladder.....	4
Cholecystitis and cholelithiasis.....	3
Empyema of the gall bladder, with stones.....	3
Acute cholecystitis with perforation and generalized peritonitis. (This case was pre-operatively diagnosed as appendicitis.).....	1
Total.....	11

*Diagnosis at Operation:* In only 14 or 44 per cent of these 32 cases was the diagnosis of malignancy made even at the time of operation, a fact of major significance. The reason for this may be due to the fact that the gross appearance

of the gall bladder and its surrounding structures gave no reasonable suspicion of malignancy. In the moderately advanced case the gall bladder is usually somewhat enlarged particularly when the malignant process invades the ampulla of the gall bladder, causing obstruction at the cystic duct. The scirrhus type of adenocarcinoma usually produces a hard, shrunken almost calcareous gall bladder, which at times may retract into the liver bed, and be completely replaced by neoplastic tissue. On the other hand, in the very early cases in the non-suppurating or noninflammatory type, the gall bladder may appear to be normal. In the group of 17 cholecystectomy operations, the diagnosis of carcinoma of the gall bladder at the time of operation was made 7 times. Adenocarcinoma of the gall bladder was diagnosed in two cases where the procedure

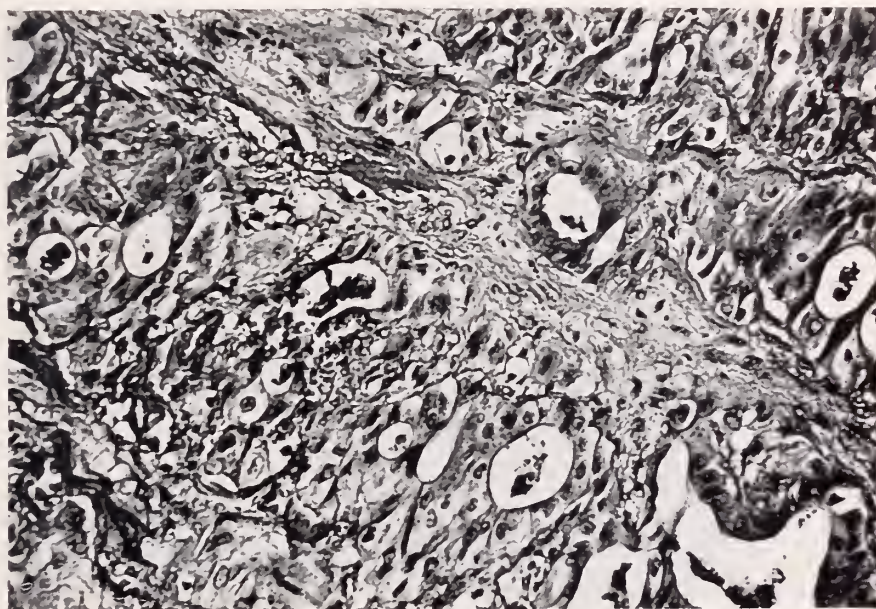


FIG. 1. J. W. (Case Z 1873). Poorly differentiated primary adenocarcinoma of the gall bladder, infiltrating gall bladder wall. H. & W. stain 320  $\times$ .

consisted of a cholecystectomy and choledochostomy. In another case where the diagnosis of carcinoma was made, a cholecystectomy and partial hepatectomy was done. In the 11 cholecystostomy operations, only 4 were diagnosed as being malignant. In the remaining 7 cholecystostomy operations, the diagnosis of acute cholecystitis and cholelithiasis, with or without empyema of the gall bladder was made. In the remaining 18 cases in this entire group, or 56 per cent, the diagnosis of carcinoma was made by microscopic examination.

*Laboratory Diagnosis:* A diagnosis of primary carcinoma of the gall bladder was made in all 32 cases. In 10 of the cases, the diseased process extended either to the liver bed or adjacent lymph nodes. The gross appearance in the cases in which the gall bladder was removed was in a fairly large percentage of cases characteristic of primary carcinoma of the gall bladder.

Microscopically the pattern was that of an adenocarcinoma of varying degrees of differentiation, or of an anaplastic carcinoma. In all instances, the gross and microscopic findings were considered by the pathologist to be those of primary carcinoma of the gall bladder, or entirely consistent with this diagnosis.

By way of illustration, Figures 1, 2 and 3 are photomicrographs of representative sections. Figures 1 and 2 show infiltrating adenocarcinomas. Figure 3 indicates blood vessel invasion in a case of adenocarcinoma of the gall bladder.

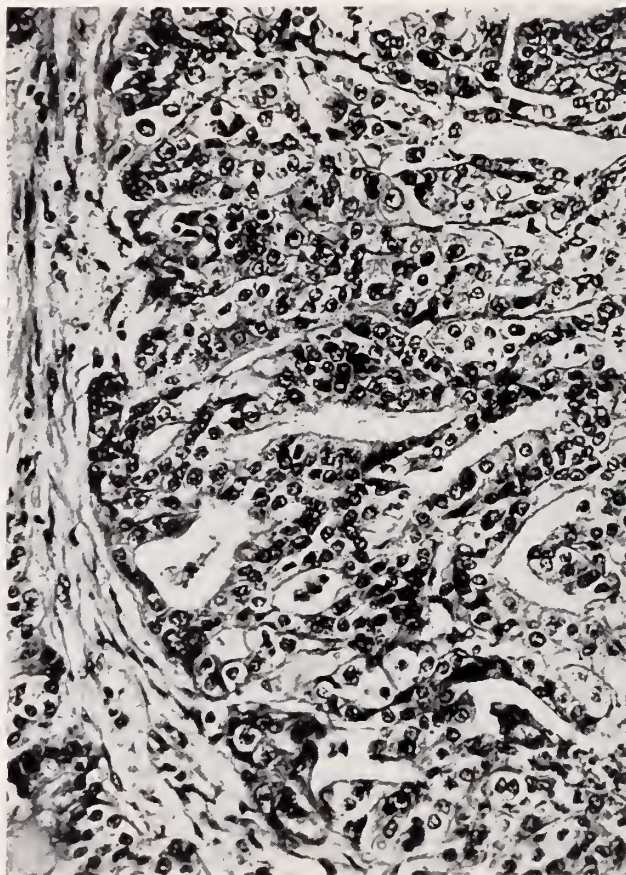


FIG. 2. A. S. (Case No. B 12066). Poorly differentiated primary adenocarcinoma of the gall bladder, infiltrating diffusely through gall bladder wall. H. & W. stain 320  $\times$ .

*Postoperative Results:* There were 10 postoperative deaths in the hospital. These deaths occurred during a period of 4 days to 1 month, postoperatively. All were in patients who had extensive complications at the time of operation. In one case, death followed after a long postoperative septic course with chills, fever and jaundice. In 2 cases, death was due to gall bladder perforation with extensive peritonitis. In 3 cases, metastasis to the liver was the direct contributory cause. Hypertension with malignancy in an old woman was another



cause of death. In the remaining 3 cases, the exact cause of death was undetermined. Nineteen of these cases were listed as improved upon their discharge from the hospital. This is a most doubtful conclusion, judging from the ultimate end results. Three were listed as unimproved.

*Follow-up:* A follow-up of the 22 patients who were discharged from the hospital as improved was carried out personally by me either by contacting the personal physicians or the patient's family. Twenty died within a few months or one year

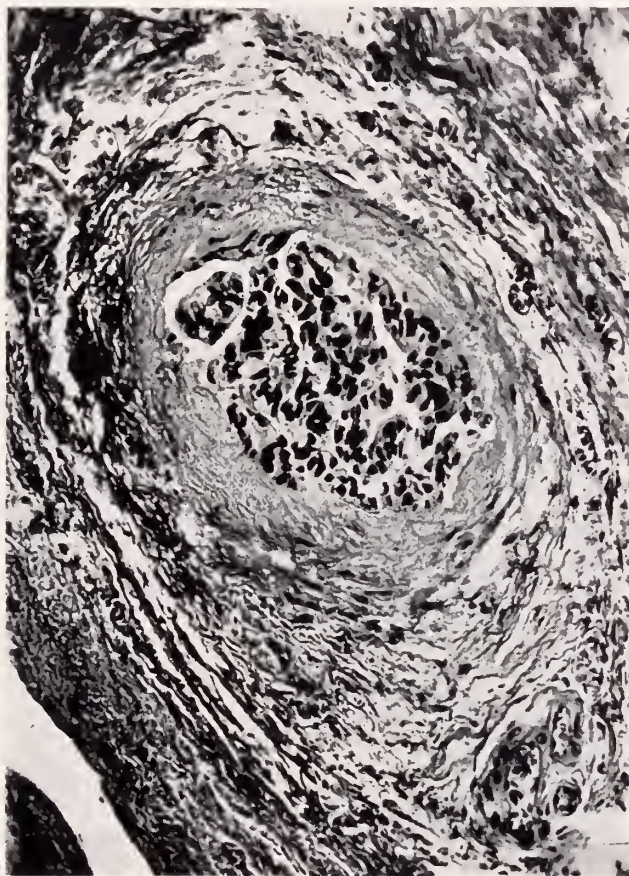


FIG. 3. P. M. (Case No. B 12819). Tumor embolus in small serosal vessel of gall bladder in case of primary adenocarcinoma of gall bladder. H. & W. stain 320  $\times$ .

after leaving the hospital. One patient was alive five years after her operation. This is rather unusual. This patient was admitted to the hospital with a diagnosis of cholecystitis of only four days duration. She gave a history of having had attacks of upper abdominal pain during the past eighteen years. Her present illness was of an acute onset. At operation a diagnosis of empyema of the gall bladder with stones was made, and a cholecystectomy was performed. The microscopic examination showed infiltrating adenocarcinoma and an acute



cholecystitis. The slides were rechecked one year ago by our pathologist and he assured me that the diagnosis of carcinoma was correct. One of the patients was alive six months after the operation. We are unable to trace her now. According to this follow-up, there is only one five year cure in this series of 32 cases, approximately 3 per cent.

#### COMMENT

In analyzing the clinical course of this group of cases, one is justified in coming to the conclusion that the treatment of carcinoma of the gall bladder at the present stage is rather discouraging, to say the least. Clinical criteria for an early diagnosis are definitely inadequate, even after diligent and painstaking clinical and laboratory studies. The diagnosis is rarely made preoperatively, and is even frequently missed at the time of operation, when the disease is in its early stage. The collective experience gathered from a much larger group of cases reported in the recent surgical literature, point to the same conclusions. Only in rare occasions may a patient's life be prolonged by a very early operation, but in most instances the end results are extremely unsatisfactory. Rarely is the patient's life prolonged more than six months to one year. Wide liver resection in cases where the disease is invading that organ has been advocated, but the end results are not sufficiently encouraging to make it a routine surgical procedure. The immediate operative deaths in partial hepatectomy combined with cholecystectomy were high, 18 per cent, and recurrence took place within a period of six months to one year (2). Only one patient in our series had a partial hepatectomy in conjunction with a cholecystectomy, but the end result was unsatisfactory.

The importance of evaluating the clinical course of carcinoma of the gall bladder consists mainly in its prophylactic value. One should consider the all too frequent association of stones with carcinoma of the gall bladder at least as one of the several indications for cholecystectomy, particularly when there is a history of several attacks of gall bladder colic, with its associated inflammatory complications. This is clearly brought out in the analysis of the case histories in our group of cases. While one cannot accept completely the theory of the direct relationship of gall stones to carcinoma of the gall bladder, neither can one entirely reject it. It should play an important part in the consideration of surgery of the gall bladder. The so-called static, or "silent gall stones," which is very often advanced as an argument against the operation of cholecystectomy in the not too troublesome cases is, in my estimation, not sufficiently convincing. When we speak of silent gall stones, we really mean temporary dormant gall stones. My personal experience with this so-called silent gall stones condition is gathered from a rather fairly large series of operations on the gall bladder and bile ducts (1000 cases), which leads me to the conclusion that permanently dormant gall stones are rather a very limited condition.

On many occasions the writer experienced in the course of some lower or mid abdominal operation, a gall bladder that contained stones. A cholecystectomy was not indicated at that time. The preoperative history pointed to another

condition for which the operation was being performed. However, a careful check with the patient of the earlier history very seldom failed to elicit a history which definitely pointed at least to a suspicion of gall bladder disease. A number of these patients returned for operation with acute or subacute symptoms of gall bladder disease as long as six to eight years after the original operation. One patient who had a cholecystostomy performed thirty years ago for stones, came back with a recurrence of symptoms and at operation a carcinoma of the gall bladder with stones was found.

With the present advances in surgery of the gall bladder, the risk of cholecystectomy in non-complicated cases is rapidly being reduced to a point where the risk of surgery as measured against the risk of procrastination with all the associated conditions that go with it, is more than balanced by early radical operation.

#### CONCLUSIONS

1. Carcinoma of the gall bladder is an insidious disease, and may be entirely painless in the early stages.
2. There are no definite clinical or laboratory criteria at present to make an early preoperative diagnosis possible in the majority of cases.
3. In its early stage, the correct diagnosis may be overlooked, even at the time of operation.
4. Malignancy should be suspected in a gall bladder if the walls are thick and friable, particularly when there is a history of repeated attacks of gall bladder colic with cholecystitis.
5. In all cases where a cholecystostomy is done, a biopsy is imperative.
6. The role of gall stones as a possible causative agent in the production of carcinoma should be considered as one of the indications for cholecystectomy.

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# EPIDERMOID CARCINOMA OF THE ANAL CANAL

## REPORT OF 28 CASES

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Since the importance of low-lying carcinoma has been stressed recently in regard to gland spread and its effect on prognosis, we have come to realize the even greater need not only for wide extirpation but, in addition, for extended excision of all gland pathways descriptively termed "pelvic lymphadenectomy".

It is not the purpose of the writers in this presentation to discuss the glandular variety of cancer located in the distal segment of the rectum, but rather to record our experience with a group in which the symptomatology, mode of extension, metastasis, prognosis and treatment, vary in some respects—namely, epithelioma of the anal region.

*Incidence.* It is common knowledge that epidermoid carcinoma is not a rarity but does occur in the lower percentage bracket. The incidence is reported in Table 1.

In 1938, one of the authors (H. E. B.) reported 68 cases in 1133 patients collected from our various services (1), an incidence of 6 per cent. During the nine year period ending September 1, 1949, of 1028 patients with cancer of the large bowel there were disclosed 28 instances of anal epithelioma, or 2.7 per cent.

*Sex, age, race.* Epidermoid carcinoma is about equally divided between males and females with a slight preponderance of the latter. In Keyes' series (22), 34 of 40 patients were females, while in our group 16, or 59.2 per cent, were females. The average age was 58.2 years; the oldest 71; and youngest, 38. A recent report from India cited an incidence of 27 per cent among the Hindus.

*Etiology.* While the cause is unknown, it is well to be mindful that cancer may be found superimposed on benign anorectal pathology. Innumerable instances have been recorded by Rosser (28, 29), Binkley (7), Smith (31) and others where this variety of tumor has occurred in external hemorrhoids, fistula, esthiomene, lymphogranulomatous venereal stricture and fissure. Keyes (22) considered leukoplasia a factor, but discarded it because of the relative frequency in females compared to males. Cattell and Williams (9) cite the presence of a previous condition of chronic irritation due to irradiation in cases of epidermoid carcinoma.

*Pathology.* There are two common varieties—the squamous-cell and the basal-cell types—although some investigators describe a third, the mixed, which presents characteristics of both. The squamous-cell variety begins in the anal epithelium and presents itself as a slight thickening or nodular elevation. It is firm, with indurated base. While at first movable, it later becomes fixed to the underlying tissues. When well developed, the tumor breaks down to form an ulcer having raised, everted and rolled edges. Although somewhat variable, the color is reddish violet, while the base is necrotic and gray. The discharge is blood-tinged, watery and irritating. There is a tendency toward crust formation, and

distinct nodules around the edge of the ulcer are common. Superficial extension along the perineum to the scrotum or the vulva is frequently encountered. The basal-cell variety is rare, only a few cases having been cited in the literature. Ordinarily this variety of carcinoma begins as a small nodule in the dermis. It grows slowly and gradually ulcerates onto the surface. In the two cases in our series, the ulcer was ragged, the base irregular and angry with the edges somewhat elevated and rolled. Induration was conspicuously present.

*Location.* All epidermoid lesions in our group were located in the anal canal although unusual sites have been reported in the descending colon by Keyes (22) and in the rectosigmoid by Thiele (35) as well as by Cattell and Williams (9). While little is known of the cytogenesis and the behavior of these growths, the most tenable hypothesis is that they arise from embryonic tissues which are mis-

TABLE 1

AUTHOR	TOTAL SERIES	NO. CASES	PERCENTAGE
Gabriel (12).....	1700	55	3.3
Buie & Brust (8)...	352	51	1.7
Raiford (27).....	352	10	2.8
Lawrence (23).....	635		3.3
Kerr (20).....		80	5.0
Kaplan & Rubenfeld (19)...		8	4.6
Cattell & Williams (9)...	600	10	1.7
Funke (11).....			4.0
Gazetta & Cole (13).....	100		4.0
Keyes (1937) (21).....			5.0
Keyes (1944) (22)...		40	5.7
Meland (24).....	260	17	6.0
Quenu (26).....			20.0
Sweet (33).....	802	38	4.7
Bernstein (3).....	218	6	2.8
Halpert, Murdoch & Young (16)...	150	9	6.0
Bacon (collected 1938) (1).....	1133	68	6.0
Bacon, Venturo & Sauer.....	1028	28	2.7

placed during development. It has been explained on the theory that regenerative cells of the epithelium have the property to produce either a secretory (glandular) or a protective (squamous) epithelium. Hosler and Murphy (18) cited two instances of adenocarcinoma involving the anal region. Scarborough (30) encountered a primary adenocarcinoma of the anal gland, while Thompson (34) resected a descending colon lesion which disclosed histologic evidence of both squamous-cell carcinoma and adenocarcinoma.

*Metastasis.* Metastasis from basal-cell carcinoma is practically nil, whereas in the squamous-cell variety, it does occur but less frequently and less widely than does adenocarcinoma. Locally it is more invasive but grows more slowly. The mode of spread of epidermoid cancer is by continuity, contiguity, lymphatics and through the blood stream. Local extension to the anal sphincters, perianal tissues, rectovaginal septum or prostate is common. Lymphatic metastasis oc-



curs by way of the downward zone (anal and perianal skin, ischiorectal fat) and the lateral zone (lateral ligaments, pelvic fascia, Denonvilliers' fascia, base of urinary bladder, pelvic peritoneum, cervix and base of broad ligament). While the lymph for the most part is drained through the perineum into the inguinal nodes, it should be recognized that metastasis does occur by way of the lateral and the superior zone of spread. A few instances have been observed in our own series and many have been cited in the literature (21, 9, 12, 14). Metastasis to the liver from squamous cell carcinomata has been reported also (2, 5, 8, 20, 27).

*Gradation of tumor.* There appears to be considerable variation in the gradation of tumor. In Kerr's (20) series using Broder's classification, 4 were grade I, 17 grade II, 41 grade III and 18 grade IV. Employing Dukes' classification, Gabriel (12) noted that 22 were of low grade, 21 of medium grade and 12 of high grade. In our group, the majority were grade II as shown:

Grade	Number
I.....	1
II.....	14-51.8%
III.....	11
IV.....	2
Total.....	28

*Symptoms.* A history of a lump beside or at the anal margin is not uncommon. Strangely enough seven of our group had been operated upon shortly before our examination for hemorrhoids or fistula, and the diagnosis was somewhat difficult. Bleeding was cited by 13 patients, or 48.1 per cent. Only in the incipient stage is pain or discomfort absent. In our series, pain was described as the first symptom in 12 instances, or 44.4 per cent. As infiltration occurs and the muscles are invaded, the pain becomes tormenting and at times is of an excruciating nature. Tenesmus is, of course, common. Frequent desire for and incompleteness of evacuations, ribbon-shaped stools and a sensation of fullness and pressure are usually cited. Incontinence is frequent, so that irritation of the surrounding skin from the discharges is encountered. A tender or even painful mass in the groin may be mentioned, while late in the disease loss of weight is described. Strangely enough the duration of symptoms with anal cancer is approximately six months longer than with cancer of the rectum.

*Diagnosis.* The diagnosis of anal carcinoma is made on the presence of a nodular elevation in the anal lining which is usually pearly gray in appearance. The ulcer is fairly characteristic, although hypertonicity of the anal sphincters may interfere with the interpretation. The base appears angry and is frequently covered by a dirty slough. The edges are nodular, rolled and somewhat everted. Hardness and fixation to the underlying tissues are, with nodularity, pathognomonic of a malignant growth. It is our custom to remove a specimen for examination in every case, not only to confirm our clinical diagnosis but also for gradation of the tumor.

*Treatment.* While it is recognized that surgical extirpation by the abdominoperineal route is the only procedure to be recommended for adenocarcinoma of the

lower rectum, there still exists some controversy as to the best approach for basal-cell and squamous-cell carcinoma of the anus. Many investigators prefer irradiation to surgery because of the accessibility of the lesion. Pruitt (25), for example, cites good results in these squamous-cell carcinomata from using needles containing 1.33 milligrams of radium into and around the growth, including the ischio-rectal fossa. The needles are left *in situ* from four to six days, or until a dosage of

TABLE 2  
*Authors' Series (1941-1949)*

NUMBER	INITIAL	AGE	SEX	TYPE	GRADE	ABDOM- INOPE- RINEAL EXCI- SION (MILES)	COLOS- TOMY PERI- NEAL EXCI- SION	COLOS- TOMY ALONE	ROENT- GEN THER- APY	RADIUM	INGUI- NAL NODE DISSEC- TION	RE- FUSED TREAT- MENT
1	G. B.	49	F	Squamous	2	—	yes	—	yes	—	—	—
2	A. C.	71	F	"	2	yes	—	—	yes	—	—	—
3	E. S.	56	M	"	2	—	yes	—	yes	—	yes	—
4	O. N.	52	F	"	3	—	yes	—	yes	—	yes	—
5	C. R.	43	M	"	3	—	yes	—	yes	yes	—	—
6	A. L.	67	M	"	3	—	yes	—	yes	—	—	—
7	C. H.	59	M	"	4	—	—	—	—	—	—	yes
8	H. A.	69	M	"	3	—	—	yes	—	—	—	—
9	G. K.	64	F	"	4	yes	—	—	yes	—	—	—
10	R. M.	60	M	Basal	2	yes	—	—	—	—	—	—
11	B. B.	52	F	"	2	—	—	—	yes	—	yes	—
12	S. S.	39	M	Squamous	2	yes	—	—	—	—	—	—
13	M. C.	43	F	"	2	yes	—	—	—	—	—	—
14	M. K.	38	F	"	3	yes	—	—	—	—	—	—
15	J. T.	38	F	"	2	yes	—	—	—	—	—	—
16	H. H.	65	F	"	3	yes	—	—	—	—	—	—
17	T. J.	49	M	"	2	yes	—	—	—	—	—	—
18	A. A.	55	M	"	3	yes	—	—	—	—	—	—
19	S. S.	65	F	"	2	yes	—	—	—	—	—	—
20	S. F.	50	F	"	2	yes	—	—	—	—	yes	—
21	J. Y.	55	F	"	3	yes	—	—	—	—	—	—
22	J. B.	46	F	"	4	yes	—	—	—	—	—	—
23	J. S.	61	M	"	1	—	yes	—	—	—	—	—
24	J. L.	55	F	"	2	yes	—	—	—	yes	—	—
25	C. A.	55	M	"	3	yes	—	—	—	—	—	—
26	L. L. S.	65	F	"	2	—	yes	—	yes	—	—	—
27	O. B.	53	F	"	3	yes	—	—	—	—	yes	—
28	E. C.	53	F	"	3	yes	—	—	—	—	—	—

from 2,000 to 4,000 milligram-hours is given. In addition, external radiation is administered over the sacrum, the perineum and the inguinal regions so that approximately 9,000 milligram-hours are given posteriorly and 7,000 milligram-hours anteriorly over each inguinal region. Souttar (32) employs a molded apparatus containing from 120 to 160 milligrams of radium and applies it from 15 to 18 days. The inguinal glands on each side receive a similar application. Binkley (6,

4), however, advises external radiation of high voltage roentgen rays and radium rays to be followed by the interstitial implantation of gold-filtered emanation seeds. In some cases, Yeomans (36) combines irradiation with surgery. Three radon gold tubes of 0.3 mm. wall thickness are inserted into the tumor, followed by radical excision in from two to four weeks. Gordon-Watson (15) believed that if deep infiltration of the ischiorectal fossa or adjacent tissues or invasion of the inguinal gland, has not occurred, an immediate cure may be anticipated by this

TABLE 3

NO.	INITIAL	SURVIVAL PERIOD	RESULT
1	G. B.	Living 6 years	—
2	A. C.	Lived 1 year and 3 mo.	Dead
3	E. S.	Living 5 years and 8 mo.	—
4	O. N.	Lived 12 months	Dead
5	C. B.	Living 5 years and 4 mo.	—
6	A. S.	Lived 3 years	Dead
7	C. H.	(Refused treatment)	—
8	H. A.	(Colostomy alone)	—
9	G. K.	(Not followed)	—
10	R. M.	Lived 19 months	Dead
11	B. B.	Lived 9 months	Dead
12	S. L.	—	(Died following operation)
13	M. C.	Living 2 years and 7 mo.	—
14	M. K.	Living 2 years and 8 mo.	—
15	J. T.	Living 2 years and 6 mo.	—
16	S. S.	Living 2 year and 4 mo.	—
17	T. J.	Living 1 year and 7 mo.	—
18	A. A.	Living 2 years and 5 mo.	—
19	S. S.	Living 2 year and 4 mo.	—
20	S. F.	Living 2 year and 3 mo.	—
21	J. Y.	Living 1 year and 10 mo.	—
22	J. B.	Lived 9 months	Dead
23	J. S.	Living 13 months	—
24	J. L.	Living 5 years and 8 mo.	—
25	C. A.	Living 2 years and 5 mo.	—
26	S. S.	Lived 1 year and 11 mo.	Dead
27	O. B.	Living 7 mo.	—
28	E. C.	Living 6 mo.	—

method. Harvey (17) is of the opinion that for small growths two centimeters in diameter or less, radiotherapy may be justifiable in order to avoid radical removal. For large growths and those with metastasis, he recommends radical extirpation of the anus and rectum with removal of the inguinal nodes. Both Cattell (9) and Gabriel (12) believe that surgical excision followed by radical inguinal dissection offers the best prognosis.

It is our opinion that each patient with epidermoid carcinoma should be evaluated carefully and that treatment should be instituted as follows:

1. Surgical excision: The procedure of choice is an abdominoperineal excision with a permanent abdominal colostomy. The degree of extirpation should be sufficiently wide to include the three pathways of lymphatic spread—upper, lateral, downward—together with a wide expanse of the perianal, perineal and coccygeal skin, all ischiorectal fat and, in the female, the posterior vaginal wall. Another type of procedure to be considered is colostomy and posterior excision after the method of Lockhart-Mummery, but any restorative surgery for this variety of tumor is definitely contra-indicated, even though good results have been reported by Fischel and Babcock.

2. Immediately at the completion of the operation, radium in the form of gold-filtered emanation seeds are implanted interstitially. These seeds are placed into the obturator and the stumps of the anterior levator muscles.

3. Usually from 10 days to two weeks later, radical bilateral inguinal dissection is undertaken.

A review of our records shows that 25 patients were subjected to a combined abdominoperineal type of excision. There was one hospital death following resection (case No. 2) a mortality of 4.1 per cent; one died (case No. 8) following the performance of an inguinal colostomy.

Sweet (33), in a recent review of 77 cases of epidermoid cancer, observed that 13, or 17.3 per cent, survived the five year period. Radical surgery produced cures in 25 per cent, and if those untraced and those whose operations were performed less than five years after inception are excluded, the percentage of five year cure is 28.8. On the other hand, by irradiation, cure was effected in only 5.2 per cent. Of 17 patients treated by Keyes (22), cites a five year survival rate of 20 per cent in his group of 55 cases.

In our group of patients, one refused treatment (case No. 7); a colostomy alone was performed in another (case No. 8); roentgen therapy and inguinal node dissection was instituted (case No. 11) and it is known that this patient died 9 months later. The remaining 25 patients were subjected to an abdominoperineal excision. Of their number all have been followed with the exception of case No. 9.

The period of survival of these 24 patients is shown in Table 3.

#### SUMMARY AND CONCLUSIONS

Twenty-eight cases of epidermoid cancer of the anus are presented. An incidence of approximately four per cent was found as the average among the various references consulted.

While several authors consider benign anorectal pathology as an etiologic factor, it is difficult to ascertain whether it should be accepted as carcinogenic or merely coincidental. Irradiation is perhaps the only one that can be looked upon as such. Regional metastases are prone to occur in the three different pathways, but the downward and lateral spread appears to be more important than with adenocarcinoma of the rectum.

Since both the downward and the lateral pathways are more difficult to eradi-



cate, the poor prognosis of these tumors suggests lack of radicability of our present methods of extirpation. Inguinal and pelvic node dissection should prove to be necessary for removal of all the lymph node bearing area.

Irradiation is advocated by some authors, but surgery alone or supplemented by irradiation is receiving the approval of the majority.

Irradiation alone may seemingly present almost the same results as surgery but this is not decisive proof of its validity, because even if the tumor can be destroyed, the metastases are not influenced by it. This shows that further studies are necessary, and resection of lymph-bearing areas should be more correctly evaluated.

It is the authors' opinion that the best treatment available is abdomino-perineal excision and irradiation, together with inguinal node dissection, from seven to ten days after the operation. Not only should the inguinal nodes be eradicated but both the external and the internal iliaes should be stripped.

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# THE PRESENT STATUS OF THE SURGICAL TREATMENT OF CANCER OF THE COLON AND RECTUM\*

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Notwithstanding considerable controversy over the relative merits of various operative techniques, the general trend in the surgical treatment of carcinoma of the colon and rectum has become definitely more radical in scope. This fact is expressed in the literature in terms of a progressive increase in the index of operability, and the performance of wider resections of involved bowel segments and associated zones of regional metastatic spread. It is noteworthy, however, that in spite of the more extensive nature of the surgery performed, there has also been reported a concomitant decline in postoperative morbidity and mortality, and improvement in long-term survival rates.

Several factors have contributed to the achievement of these results namely, earlier diagnosis, hence earlier treatment; improved preoperative preparation and postoperative care, including chemo- and antibiotic therapy; and the technical application of newer knowledge regarding the anatomy of the large bowel and the areas of metastatic spread of malignant lesions encountered therein.

## DIAGNOSIS

Educational campaigns in recent years, sponsored by various agencies and mediated through the press and radio, have awakened considerable public interest in the problem of cancer in general. Undergraduate and postgraduate teaching in medical schools and hospitals has also stimulated the medical profession to a keener evaluation of the warning signs of malignant disease. Unexplained anorexia, weight loss or anemia, recurrent abdominal pain, change in individual bowel habit, or rectal bleeding are symptoms which demand prompt clinical investigation to determine their cause. It is well known that most malignant lesions of the lower bowel (anus to lower sigmoid colon) are easily accessible either to the examining finger or to visualization by the simple procedure of sigmoidoscopy. Tumors situated at higher levels may be readily detected with a high degree of accuracy by means of the barium enema and air-contrast roentgenographic examinations.

Adenomatous polypi which are widely believed to possess malignant potentialities may be similarly demonstrated and their prompt extirpation recommended as a prophylactic measure.

Factors which contribute to complications and poor results in the surgery of large bowel cancer include anemia and debility, obstruction, mural penetration of the growth with fixation to and involvement of contiguous viscera, perforation with resultant peritoneal infection or local abscess formation, and metastatic lymphatic and venous spread. Thus, early diagnosis and institution of treatment without delay assume paramount importance in any consideration of the problem of carcinoma of the large bowel. For example, Collier and Ransom

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(1) noted that with earlier diagnosis they were able to lower the mortality rate for cancer of the rectum as well as appreciably increase the resectability rate.

#### PRE- AND POSTOPERATIVE CARE

There is no doubt that much of the success of modern surgery is to be attributed to the practical application of the newer knowledge regarding the various biochemical and physiological changes which accompany disease processes and occur in patients subjected to surgery. The past 25 years have witnessed a marked shift in emphasis from purely technical considerations to the elucidation of many problems related to the general supportive care of the patient before, during and after operation. This holds true in all fields of surgery, and is particularly applicable to that of cancer of the colon and rectum which is so often complicated by various mutually related clinical problems secondary to the lesion itself, as well as by those resulting directly from the operative procedure undertaken for its extirpation. These problems include fluid and electrolyte depletion, anemia, protein and vitamin deficiencies, the effects of intestinal obstruction, the control of infection, and the appraisal and treatment of concomitant cardiovascular or renal complications.

It is now a cardinal principle of large bowel surgery that the resection of an obstructing tumor may not be attempted until adequate proximal decompression has been accomplished and the bowel adequately prepared by cleansing lavages and the administration of chemotherapy. Although long-tube decompression has proved to be of great value in the management of small bowel obstruction, it may be used in obstruction of the colon only under the circumstance in which, from the roentgenographic examination, one can be certain that the ileocecal valve is incompetent, thus permitting retrograde passage of gas and fluid from the colon into the small bowel. With competency of the ileocecal valve, however, a distal blockage of the colon produces in effect a closed-loop obstruction which, if unrelieved by transverse colostomy or cecostomy, eventuates in a fatal peritonitis secondary to distention gangrene and rupture of the bowel wall.

In 1939, Garlock and Seley (2) demonstrated clinically and bacteriologically that following the pre-operative oral administration of sulfanilamide, there was a marked reduction in the bacterial activity in the colon, and they suggested its routine use in preparing patients for operations upon the large bowel. This has been amply confirmed by many other observers, who have reported an appreciable decline in the incidence of postoperative peritoneal and wound infection. With rare exceptions, the use of chemotherapeutic and antibiotic drugs in colonic surgery has become almost universal (Turell (3), Turell and Lyons (4)).

Because of various toxic reactions observed with the use of the readily soluble sulfonamides, newer drugs have been synthesized which are but poorly absorbed from the intestinal tract. The most commonly used of these is succinyl-sulfathiazole (sulfasuxidine). Although it possesses less bacteriostatic power than phthalylsulfathiazole (sulfathalidine), it has been found to be more helpful in



the mechanical cleansing of the bowel since it renders the stools more fluid and less tenacious in consistency. The latter drug seems to find more usefulness in the treatment of the bacterial dysenteries.

It has been variously stated that the recent tendency to return to one-stage colonic resections has been made possible by the employment of orally administered slightly soluble sulfonamides (Coller and Berry (5), Behrend (6)), and that the modification of the bacterial flora of the colonic contents favors early healing of the anastomotic suture line, and reduces the incidence of post-operative peritonitis and wound infection (Poeth (7)). Comparative studies have also shown a marked reduction in the incidence of surgical infection and mortality (Bell (8), Pemberton (9)). Pemberton, at the Mayo Clinic, noted a reduction in mortality from between 15 and 20 per cent before 1939, to about 5 per cent since using oral sulfonamides in the pre-operative preparation of the patients. This is particularly noteworthy since the decline in mortality was accompanied by an appreciable increase in surgical resectability rates.

Streptomycin, orally administered, has also been demonstrated to be efficacious in inhibiting colonic bacterial activity (Zintel et al. (10)). However, since many organisms tend to rapidly develop resistance to this drug, it is recommended that it be used for only a short time namely, about 2 days prior to operation (Nichols and Herrell (11)). Bacon and Roe (12), and others, suggest that streptomycin and sulfasuxidine be used in combination.

Chemo- and antibiotic therapy have also been recommended for prophylactic use during the postoperative period (Ravdin, Zintel and Bender (13)).

#### TECHNIQUE

In recent years there has accumulated from many surgical clinics a considerable literature regarding the relative merits of various operative procedures now advocated for the extirpation of malignant tumors of the colon and rectum. Fundamentally, however, the trend in many respects represents a return to popularity of basic techniques which were described originally many years ago during the latter part of the 19th and beginning of the present centuries.

The historical evolution and development of this field of surgery have been described in detail in interesting papers by Rankin (14), and Maes and Essrig (15), from which the following summary is briefly outlined. Employing the posterior (perineal) route, Lisfranc (16), in 1826, was the first surgeon to accomplish successful extirpation of the rectum. Kraske (17), in 1885, recommended removal of part of the sacrum for the purpose of better exposure. Three years later, Allingham (18) modified the operation by attempting to preserve the anal sphincters, and Hochenegg (19) described the so-called "pull-through" maneuver to bring down the proximal rectal segment, after resection of the tumor, to create a sacral or perineal anus. While attempting to resect a rectal tumor from below, Czerny (20), in 1883, because of technical difficulties encountered, found himself obliged to open the abdomen in order to mobilize the bowel from above, thus performing the "combined abdomino-perineal" operation which Mammell (21) and Quenu (22), a few years later, were to recommend as

an elective procedure. Shortly thereafter, in 1901, Mann (23) advocated abdominal "anterior resection" and primary anastomosis for rectal lesions located proximal to 2 inches above the anus. Tuttle (24) on the other hand, stated in 1903 that complete removal by the anterior route alone was attended with many difficulties in cases in which the tumor was situated well below the promontory of the sacrum in that portion of the bowel only partially covered by peritoneum. The classical radical abdomino-perineal resection for rectal cancer was described by Miles (25) in 1908, the rationale for this procedure being based, apparently, upon an appreciation of the necessity for wide removal of proximal, lateral and distal metastatic spread from the primary focus. This operation became the standard for many years, and is still practiced almost routinely in many clinics throughout the world. However, Babcock (26), Bacon (27) and their adherents have re-awakened interest in abdomino-perineal "pull-through" techniques designed to save the anal sphincters and avoid abdominal colostomy. Horsley (28), Dixon (29), Wangenstein and Toon (30, 31) and others, have become protagonists of the procedure of anterior resection for cancer of the lower bowel.

The early operations devised to remove cancer bearing segments of the colon situated above the level of the rectosigmoid junction consisted essentially of resection with open end-to-end anastomosis performed in one stage (Reybard, 1844 (32); Kohler, 1882 (33)). This technique, however, was apparently attended by a high incidence of morbidity and mortality (60 per cent mortality in a series of 17 cases reported by Billroth (34) in 1889). The multiple-stage exteriorization procedure came into vogue soon thereafter (Block (35), 1892; Paul (36), 1895), and in 1903 Mikulicz (37) reported a series of 24 cases so operated upon with a markedly reduced mortality rate of 16.6 per cent, thus establishing the operation upon a firm practical basis. Because of its safety and technical simplicity, the Mikulicz operation gained almost universal acceptance, and was practiced for many years. Rankin (38, 39), in 1928, further modified the multiple-stage exteriorization operation by devising the so-called "obstructive resection". During the past decade, however, there has been a gradual and progressive return by many surgeons to the single-stage colonic resection with primary end-to-end anastomosis, although staged obstructive resections are still employed by some under certain indicated circumstances (Garlock and Klein (40)).

Nevertheless, no matter which type of operative procedure is favored for the treatment of a lesion in a particular bowel segment, there is now a definite tendency toward the recommendation that the resections be more radically executed (McKittrick (41), Grinnell (42), Lockwood (43), Gilchrist (44)). This attitude is based upon the anatomical studies of Jamieson and Dobson (45), Rouviere (46), Westhues (47), Gilchrist and David (48, 49, 50), Collier, Kay and MacIntyre (52), Grinnell (42) and others who have studied the pathways and extent of lymphatic spread from the primary tumor focus in the bowel. Lymphatic metastasis from cancer of the colon and rectum is considered to be primarily embolic to regional lymph nodes. Usually the direction of spread is

proximalward, through lymph channels along the course of the superior hemorrhoidal and inferior mesenteric blood vessels and their branches. However, when lymph nodes become blocked by tumor cells, alternate routes of spread may be involved; thus metastatic involvement may also be found in lymph nodes situated at a level distal or lateral to the site of the primary lesion. There is ample clinical and pathological evidence to show that lymph node involvement bears a direct relationship to recurrence and long-term survival rates (Gilchrist and David (51)). In the light of these facts, it is therefore manifestly important to attempt to remove as much of potentially involved regional lymphatic areas as possible when resecting a particular bowel segment for malignancy.

When dealing with tumors of the right colon proximal to the hepatic flexure, resection of the terminal ileum and right colon to mid-transverse colon is recommended, ligating the ileocolic and right colic vessels close to their origin from the superior mesenteric, being careful not to traumatize the vascular supply to the small bowel. Where the lesion is situated at the hepatic flexure or proximal transverse colon, the resection should be carried out to the left of the mid-transverse colon, ligating also the middle colic vessels. High ligation of the middle colic and left colic vessels should be performed when resecting lesions of the distal transverse colon and splenic flexure, thus insuring wide mesenteric excision (41, 42). Resection of the descending colon or sigmoid should include division of all sigmoidal vascular branches as well as branches of the left colic, and the superior hemorrhoidals; the resection then would include a large bowel segment extending from the splenic flexure or descending colon to the upper rectum. Rectosigmoidal tumors would include a similar wide dissection (42, 44). When performing abdomino-perineal resection, it is recommended (43, 44) that the dissection include the inferior mesenteric vessels above the left colic branch to permit removal of bowel up to the descending colon or splenic flexure, fashioning the permanent colostomy at this level. Abdomino-perineal resection should include wide lateral excision of the levator ani muscles in order to eradicate possible lateral extension via the lymphatic channels on the superior surface of these structures (43).

*Operations for Carcinoma of the Right Colon:* Person and O'Neill (53), in a recently published article in which they evaluate various operations for carcinoma of the right colon, state that they favor a one-stage resection including terminal ileum, cecum, ascending colon, hepatic flexure and right half of the transverse colon, with primary aseptic end-to-end suture according to the method of Scarff. They feel that the obstructive resection operation for the right colon, as recommended by Lahey (54), Carter, Slattery and Hahn (55), and Patterson and Webb (56), has the following disadvantages: 1) long period of hospitalization; 2) excoriation of the skin caused by the irritating ileal discharge; 3) higher incidence of wound infection, postoperative incisional hernia and abdominal wall recurrence. The method is also said to be limited, (Sistrunk (57)), in cases in which the mesentery of the colon is short and difficult to mobilize, as well as in large, adherent growths with infection, perforation and obstruction.

Another type of staged procedure for carcinoma of the right colon consists of

a preliminary ileo-colostomy, followed in about two or three weeks by resection of the terminal ileum and right colon as employed by Pemberton and Whittaker (58), Dixon and Priestley (59), Ransom (60), Allen (61), Garlock and Klein (40). Person and O'Neill (53) point out, however, that the trend among many surgeons is now toward operation in one stage (Mayo and Schlicke (63), Rankin (62), Harvey (64), Cheever (65), MacFee (66), White and Amendola (67). It is claimed that this operation is technically easier, since the surgeon is unhampered by adhesions resulting from a previous operation. The patient is subjected to only one operation and anesthesia, and the morbidity, hospitalization and mortality are therefore reduced. Person and O'Neill believe that the one-stage operation is followed by a smoother convalescence and that it decreases the hazard associated with leaving the malignant tumor in the body a longer time. According to the experience of Garlock and Klein (40), however, many patients with tumors of the right side of the colon are in a markedly depleted condition when admitted to the hospital, usually with a severe secondary anemia and considerable disturbance in protein metabolism. In spite of every effort at adequate and thorough pre-operative rehabilitation, these patients still represent relatively poor operative risks, so that it is considered wiser, in many of these cases, to stage the resection. They do not agree with the statement that it is more hazardous to subject the patient to two surgical sessions, for in a group of 72 patients treated by the two-stage operation, there was only one death following the first procedure. While it is, of course, preferable to do the operation in a single stage when it can be accomplished with safety, mortality will be avoided by using the two-stage procedure in poor-risk patients.

*Operations for Carcinoma of the Left Colon:* As noted by Turell and Lyons (4) in their review of the literature of colonic and proctologic diseases, the present day tendency in many clinics in the treatment of colonic carcinoma is definitely toward the return to the one-stage resection with primary anastomosis. The proponents of primary resection believe that more radical removal of bowel and regional lymph nodes is possible by means of this technique than with exteriorization resection procedures, that employing a one-stage operation reduces the length and expense of the hospital stay and that the complications of exteriorization, such as retraction of either or both bowel loops, prolapse, infection, wound disruption and incisional hernia are reduced.

There is also considerable argument over the relative merits of the open anastomosis versus the closed so-called aseptic types of bowel suture, as well as the advisability of performing a complementary vent colostomy proximal to the anastomosis. As far as the methods of re-establishing continuity of the bowel are concerned, both types seem to be quite successful and satisfactory in the hands of the respective surgeons who use them. More important than the use of a particular type of anastomosis is the observance of fundamental principles of intestinal suture, as defined by Whipple (68), consisting of careful preservation of the blood supply to the bowel to be sutured, accurate placing of fine sero-muscular sutures to provide adequate peritoneal apposition along the suture line, and avoidance of tension on the suture line with its accompanying tissue



necrosis, by keeping the proximal segment of bowel empty of gas and fecal content. We routinely use complementary tube cecostomy as a proximal vent after primary colonic resection and anastomosis, including anterior resection of tumors of the distal colon. It is a simple maneuver, requires but a few minutes to perform and the small McBurney incision heals rapidly and spontaneously after the tube is withdrawn. Although it is true that many cases do well without a complementary proximal vent, we feel it is good insurance against the occasional occurrence of postoperative obstruction due to edema at the anastomosis. Prevention of proximal distention in this way will avoid tissue necrosis and leakage at the suture line.

Jones (69), Lahey (70), Garlock and Klein (40), and others feel that the multiple-stage obstructive resection type of operation still has a place in the armamentarium of the colonic surgeon. On the basis of extensive experience with the procedure, they are of the opinion that as adequate a cancer operation can be performed by this method as with the operation of resection and primary anastomosis. If one mobilizes the splenic flexure, frees the descending colon from its lateral peritoneal attachments, and similarly mobilizes the rectosigmoid colon and upper rectum, it becomes an easy matter to remove large sections of the left colon in accordance with the principles of adequate eradication of cancer bearing bowel and associated zones of lymph node drainage. Since the advent of chemotherapeutic and antibiotic drugs and more effective general supportive and replacement therapy, Garlock and Klein have also been doing single-stage resections with greater frequency. Nevertheless, they still utilize the operation of obstructive resection under certain indications, namely, 1) marked disproportion in the size of the bowel above and below the tumor due to chronic obstruction; 2) pericolic infection due to penetration and perforation of the lesion; 3) obesity, when it is difficult to accurately delineate the mesenteric vascular tree supplying the bowel; 4) advanced age or poor condition of the patient, when it is felt that it is safer to execute the operation as rapidly as possible in order to avoid prolonged anesthesia and tissue manipulation.

*Operations for Carcinoma of the Rectosigmoid and Rectum:* At the present time there is marked difference of opinion as to which operative procedures are to be preferred for the extirpation of cancer of the rectosigmoid colon and the rectum. Excluding the relatively limited Hartmann and Lockhart-Mummery operations which have their special indications in aged or poor-risk patients, there are three main types of operative procedures generally employed for lesions of the distal bowel: 1) The classical Miles abdomino-perineal resection, in which the lower sigmoid, rectosigmoid, rectum and anus together with the levator ani muscles and regional lymph node areas are removed, and permanent abdominal colostomy performed. Recently, higher resection to the level of the descending colon or splenic flexure has been advocated under conditions of extensive lymph node involvement (Grimmell (42), Lockwood (43), Gilchrist (44), Rosi (71)). 2) Anterior resection, which implies segmental resection of involved bowel with primary anastomosis of peritoneum-covered colon to non-peritonealized rectum. 3) Abdomino-perineal resection with preservation of the anal sphincters, utilizing the Hochenegg "pull-through" principle.

In the light of the clinical and pathological studies noted above, many surgeons insist that only the Miles operation is sufficiently radical in scope to insure the widest possible excision of potentially involved areas of regional metastatic spread. These areas include lymph nodes above and below the level of the tumor, the lymphatic pathways which extend laterally on the superior surface of the levator ani muscles, and local venous channels which may be left behind if the lower rectum is preserved for anastomotic procedures.

The more conservative anterior resection for rectosigmoid and rectal cancer has been subjected to considerable clinical trial in the hands of many surgeons in recent years. It was hoped that radical removal of the disease could be accomplished without sacrificing the anal sphincter mechanism. On the basis of follow-up studies, however, Wangenstein and Toon (30) have concluded that the operation is not suitable for lesions situated at 8 cm. or less from the anus because of the high incidence of local recurrence, particularly in the area of lateral spread rather than at the suture line. The operation is recommended for tumors situated from 14 to 20 cm. from the anus, since no recurrence was noted following anterior resection at this level. Lesions in the intermediate area between 9 and 13 cm. from the anus comprise a controversial group in which these authors feel that with proper selection of cases, the sphincter saving operation may be used in many instances.

In a recently published report on a follow-up study of a series of 163 cases of anterior resection, Garlock and Ginzburg (72) feel convinced that this sphincter saving operation should rarely, if ever, be employed for cancer of the rectum situated below the level of five inches (approximately 12.5 cm.) from the anal margin because of the inability of the surgeon to excise sufficient rectum distal to the tumor, (at least 2 to 3 inches), to meet the requirements of radicality demanded in the performance of a good cancer operation. On the other hand, they state that it is not necessary to perform abdomino-perineal resection for all cancers of the rectosigmoid, and that, when local conditions permit, it is possible to carry out as thorough an operation with preservation of the anal sphincter with a negligible incidence of local recurrence. These authors define the surgical rectosigmoid as that area of the bowel where the meso-sigmoid ceases to exist as such, where the peritoneum, instead of encircling the bowel leaves the posterior and lateral aspects and merges with the pelvic peritoneum, and where the inferior mesenteric vessels, now the superior hemorrhoidals, leave the mesentery of the sigmoid and lie behind the bowel. In most individuals this point of convergence lies opposite the second or third sacral segments. In the person of average height and average shaped pelvis, the rectosigmoid is located between 6 and 8 inches from the anal margin, less in short, squat persons, more in tall, lanky individuals.

Gilchrist (44) advises the most radical procedure possible, namely the Miles type of abdomino-perineal resection with division of the superior hemorrhoidal vessels at least  $1\frac{1}{2}$  inches above the promontory of the sacrum, and widest possible resection of the levator ani muscles and their accompanying lymphatics for adeno-carcinoma of the rectum which lies entirely or partially below the reflection of the peritoneum from the anterior surface of the rectum to the bladder

in the male, the uterus in the female. In carcinoma of the rectum where the bowel containing the tumor is completely covered by peritoneum anteriorly and where the tumor lies below the promontory of the sacrum (apparently the surgical rectosigmoid as defined by Garlock and Ginzburg), the operative procedure advised is either anterior resection or obstructive resection (David (73)) if the lymph nodes along the superior hemorrhoidal vessels are not markedly enlarged, if the tumor is not large, and if there is no fixation to adjacent structures or signs of obstruction. The bowel and mesentery are divided at least  $1\frac{1}{2}$  inches (or better, 2 inches) below the growth. However, if the proximal lymph nodes are enlarged and there are signs of lymphedema proximal to the tumor, or if the tumor is adherent to the adjacent structures, then an abdomino-perineal resection is done, the bowel being resected as high as the proximal part of the sigmoid colon. In cases where lymph node involvement extends to a higher level or more centrally, and these grossly or on frozen section show metastatic involvement, the inferior mesenteric artery is divided at the aorta, the soft parts dissected downward from the ligament of Treitz, laying bare the aorta, left ureter and kidney, and the descending colon, sigmoid flexure and rectum removed. The splenic flexure is then brought out as a terminal colostomy.

On the other hand, Babcock (74, 75), Bacon (27), Mandl (76) and others are of the opinion that the Hoehenegg "pull-through" procedure, with preservation of the anal sphincters is as radical as the combined abdomino-perineal resection of Miles. Hemicolectomy and proctosigmoidectomy with transplantation of the sigmoid, descending or even the transverse colon to the anus have been described (Bacon and Smith (78)). Babcock (74) favors perineal colostomy to abdominal colostomy; the anal sphincters are preserved where possible. However, according to some reports, it is difficult to achieve perfectly normal fecal control (Waugh (79)) and anticipated favorable results were not achieved with this operation (Daniel (80)). Bacon and Rowe (81) state that following the Hoehenegg operation, they noted an incidence of sexual impotence in the male of only 8.3 per cent compared to 95 per cent following the Miles procedure.

The comparative efficacy of the "pull-through" operation for cancer of the distal bowel from the point of view of cure, must await the results of further long-term follow-up studies.

#### SUMMARY

Predicated upon a better understanding of the pathways of lymphatic and vascular metastasis of cancer of the colon and rectum, modern trends in the surgical treatment of this disease have become more radical in concept and application. In spite of the resultant increase in the index of operability and magnitude of the operative procedures employed, there has been a marked and progressive lowering of the incidence of surgical morbidity and mortality, and improvement in long-term survival results. These achievements are ascribed to an appreciation of the importance of earlier diagnosis and treatment, the use of chemo and antibiotic therapy to control infection, decompression of obstruction and the practical application of the newer knowledge of general supportive and replacement therapy before, during and after operation.

Controversial questions regarding the operative techniques employed for resection of cancer of the colon, excepting the rectosigmoid and rectum, include the merits of single versus multiple-stage procedures, various types of anastomosis and the use of complementary colostomy. Carcinoma of the rectum and rectosigmoid are treated either by the Miles type of combined abdomino-perineal resection with abdominal colostomy, anterior resection with primary anastomosis, or the Hoehenegg "pull-through" operation, the latter two designed to preserve the anal sphincter mechanism.

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## DIRECT ARTERIOVENOUS ANASTOMOSIS

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Dr. Albert Ashton Berg has been a physician for fifty-six years, most of which time he has devoted to surgery. He has been a pioneer in advancing abdominal surgery and particularly the surgery of the stomach. After many years he now has the proud satisfaction of seeing his operative methods generally approved and adopted by the surgical profession. I am honored to add a tribute to this distinguished surgeon.

It was about 1907 that my attention was attracted to the experimental work of McGraw and Carrel, showing the feasibility of uniting cervical arteries to veins in the lower animal without interruption of the circulation. It then occurred to me that by such an operation it might be possible to decompress the very dangerous aneurysms of the thoracic aorta. It is an old hydrodynamic law that when the velocity of a liquid moving through a tube is increased, the pressure exerted by the liquid against the wall of the tube is reduced or even abolished. If the velocity is increased in limited areas, as by a constriction in the conducting tube, there the wall pressure is reduced. By reducing the velocity as it occurs in areas, where the tube is expanded, as by an aneurysm, the wall pressure is increased. Apparently this well-known law in hydraulics had not previously attracted the attention of surgeons, for slowing of the blood current by ligations or other forms of pressure, or measures to produce coagulation within the sac have been advocated for inaccessible, as well as many surgically accessible aneurysms for some hundreds of years. Keen observers like the English surgeon, Percival Pott, had noticed the ineffectiveness of such ligations, and in more recent years Dr. Halsted had given much time to experiments with ligatures or metallic bands, apparently perplexed that new aneurysms formed at times both proximal and distal to his point of arterial constriction, and that aneurysms about which he had tied every arterial branch of noteworthy size, soon began to expand and finally to rupture.

With the melancholy results from ligation for aneurysms of the aorta, many surgeons had turned to the Moore-Carradi method of intrasaccular wiring with electrolysis. The results from this method had been discouraging, since nearly one-half the patients died within three months of the operation and relatively few lived over a year.

I was impressed, therefore, that if we could establish a leak from the aneurysm by connecting a large efferent artery with an equally large vein returning blood to the heart, that the distending pressure upon the sac would be reduced not only by the more rapid escape of blood from the sac into the veins of low wall pressure but also by the increased velocity of the blood through the aneurysm. Obviously, the aneurysmal end of the divided artery should be united only to the cardiac end

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of the divided vein. A lateral or side to side anastomosis between an artery and vein leads to disastrous results, as seen in spontaneous and other arteriovenous fistulas. When, for example, an aneurysm of the aorta ruptures into the descending vena cava, a tremendous congestion of the upper half of the body follows, usually with death within ten days.

The *effects of side to side arteriovenous fistula* should be differentiated from those due to an end to end artery to vein anastomosis in the direction of blood flow. A fistula between an artery and vein leads to an accelerated heart rate and increased pulse pressure from elevation of the systolic and lowering of the diastolic pressure; an increase in the cardiac output but decrease in the stroke output, engorgement of the pulmonary vessels, increase in venous pressure and in circulating time; increased blood volume, tendency to distension of the right heart, cardiac dilatation or hypertrophy, and secondary cardiac insufficiency. Locally an arteriovenous communication causes venous stasis, edema, varicosities and serious trophic changes.

Of course, the experimental operation of carotid-jugular anastomosis could be justified only upon a patient desperately ill from the aortic aneurysm. Therefore, it was not until 1925 that a suitable patient presented himself. His aneurysm was enormous, had perforated the chest wall, and the pain was so severe, despite the use of opiates, that the man was glad to accept any risk, even exitus, for a chance of relief. In this patient the common carotid artery and the greatly dilated jugular vein were divided on the right side of the neck, the cephalic ends ligated and the cardiac ends united, end to end, with fine arterial silk. When the provisional clamps were released the jugular partially collapsed, as the high velocity of the arterial blood led to a negative wall pressure in the vein. The operation was followed by reduction in the size of the aneurysm and brought relief from the pain. The patient was then able to resume light work and lived five years, finally dying from a preexisting chronic cardiac condition. Since this time, over 50 of these operations have been done by Dr. P. J. McCarthy or myself. Of 26 personal cases, about 20 were done for aneurysm of the aorta, with 1 death from hemiplegia in an obese 70 year old Negro. Following recovery from these operations there has been a striking relief from pain. A woman, for example, although the aneurysm was small, had been bedfast for eighteen months, since effort produced severe anginoid pains. Relieved, following the operation, she was able to resume her housework during the six years she remained under observation, suggesting that the anastomosis by relieving arterial tension may also be of benefit for certain types of angina.

Experience has shown that ligation of one common carotid may lead to hemiplegia in patients with advanced arteriosclerosis, particularly in those over 50 years of age. For such patients the anastomosis may be made between the innominate, subclavian or axillary vessels. Also, the artery, through anomaly or disease, may be found with too small a lumen for the desired anastomosis, making it necessary to select an artery of larger lumen on either the right or left side of the body. From the anastomosis the blood flow from the aneurysm is increased, the wall pressure in the sac is lowered, while a part of the circulating blood re-

ceives a double oxygenation by a second passage through the lungs. The more rapid filling of the right auricle of the heart would tend, by Starling's law, to slow the heart action.

The longevity following the operation for thoracic aneurysm compares favorably with that of other operations for this very dangerous condition. One patient with an aneurysm that had perforated the sternoclavicular articulation is living and in business eleven years after the anastomosis. About a year ago he returned, for the aneurysm had started to enlarge. An end to end anastomosis was then performed, using the left axillary artery and vein, with improvement.

For large aneurysms of the abdominal aorta, I have performed an end to end anastomosis, but between the proximal ends of the divided external iliac artery and vein, in 6 cases, with 1 fatality. The external iliac artery may be ligated or divided without the secondary gangrene of the leg that usually follows ligation of the femoral artery.

#### ILLUSTRATIVE CASES

*Case 1. History.* Mr. C. N. P., aged 65, white, occupation journalist, for four years had noticed a hard mass in his abdomen which was diagnosed as aneurysm of the abdominal aorta. This caused no pain or obvious disability until September, 1940, when upon the sudden application of brakes of a public bus in which he was riding he was thrown violently against the floor of a vehicle, striking upon his back. After unconsciousness for several minutes he regained his senses, bled from the nose, and had severe headache and backache. Remains of extensive bruises on his back were still visible nearly four months later. The backache persisted for three months, after which it was succeeded by severe right-sided abdominal pain which increased in intensity and radiated to the right hip and testicle. In the latter part of December, 1940 he began to take sedatives in order to sleep, and in the fourth month the pain had become unbearable except when opiates were administered at frequent intervals. By February, 1941 the pain in the abdomen had become so great that he was taken to St. Joseph's Hospital, Kansas City, Missouri. He was then unable to sleep throughout the night, even with the aid of opiates, and was flown by airplane from Kansas City to Philadelphia for possible operative relief.

*Examination.* The patient was a rather thin, edentulous elderly man, free from edema or venous engorgement and without dyspnea on movement. The lungs were clear; the heart slightly enlarged, without murmur or arrhythmia. The palpable arteries were markedly atherosclerotic. The abdomen was distended by a large expansile mass occupying much of the left abdomen and extending a short distance to the right of the umbilicus. The femoral arteries, especially the right, were sclerotic. There was no difference in the temperature of the two legs, although the pulsation of the left dorsalis pedis and left posterior tibial arteries was slightly diminished. The blood pressure in the right arm was 192/130; in the left arm 184/112; in the right leg 180/108; in the left leg 212/138. The serology was negative. The blood examination showed: hemoglobin, 11.5 Gm.; red blood cells, 4,270,000; color index 81; white blood cells, 5450 polymorphonuclears, 68, lymphocytes 23, neutrophils 5, eosinophiles 2, basophiles 1. The urine was turbid, reddish yellow; specific gravity 1.025; reaction 6.0; with a heavy cloud of albumen; no reaction for sugar and there were a few finely granular casts to the microscopic field.

*Roentgen examination.* The abdomen with special planigraphic studies revealed the aorta and the vessels of both thighs, and showed an aneurysm of the abdominal aorta extending from the level of the second lumbar vertebra to about the level of the fifth lumbar vertebra. The right lateral margin of the aneurysmal sac was visualized at a point about 4 cm. from the margin of the spine, and the maximum bulge was seen opposite the third lumbar vertebral body. The planigraphic views clearly demonstrated the sac and it could

be delineated by ordinary films. Special soft tissue technic was employed to show the femoral arteries. There was sufficient calcium in the femorals for visualization throughout part of their course in the thighs, but complete delineation of the femorals was not obtained.

*Operation.* February 12, 1941, under spinal anesthesia, through a 10 cm. vertical upper right rectus incision, the abdomen was explored, revealing a large globular aneurysm extending from 3 cm. above the navel to the bifurcation of the aorta, and approximating the anterior abdominal wall on the right side, through elevation of the left lateral peritoneal and mesenteric leaflets so that the intestines were displaced to the left. The aorta and iliacs were atheromatous, especially the left; the aorta wide and apparently thickened above the aneurysm. The abdominal wound was closed with layer interrupted wire sutures without drainage, and a 12 cm. muscle-splitting incision was made parallel with and 2 cm. above the right inguinal ligament. The unopened peritoneum was elevated from the right iliac vessels. The external iliac artery and vein were surrounded by narrow tapes, each of which was brought through a small stiff rubber tube and clamped, after the Astley method, the vessels divided and the distal ends ligated. An end to end anastomosis was made between the heart ends of the external iliac artery and the vein, using three guy sutures and a continuous suture of fine arterial silk. The atheromatous thickening of the artery at the point of division made it necessary to resect the edges. When the tapes were loosened one leaking point was found and was closed by silk suture. No further leakage followed. The vein immediately filled and pulsated and the wound was closed, without drainage, with interrupted layer sutures of fine alloy steel wire. The iliac vein before anastomosis was large and apparently normal. The external iliac artery showed thick, nearly contiguous areas of yellow atheroma in the region of the anastomosis, measuring 2 to 3 mm. in thickness. The patient remained in good condition throughout the operation.

*Course.* Two days after the operation the right leg was warm and of good color, the toes slightly cooler than those of the left side. The pain was relieved and the patient was in excellent condition. Four days after operation the severe abdominal and testicular pain had completely disappeared, and the numbness at first felt in the right leg was no longer present. A loud bruit could be heard over the right groin.

The patient was discharged thirteen days after operation, entirely free from pain, asymptomatic and apparently in excellent condition. By April 7, or six weeks after the operation, he was working about five hours daily. After unwisely working for eight weeks he developed right heart failure with pleural effusions and massive edema of both legs and scrotum. Under treatment and paracentesis the edema of the legs and scrotum subsided and he became ambulant. An attack of auricular fibrillation in October, 1941, subsided under digitalis. There was no return of the aneurysmal pain, but there was an area of impaired sensation over the dorsum of the right foot. After the cardiac breakdown in April he gained strength and by the first of November the edema had entirely subsided and it was no longer necessary to aspirate the pleural cavity. December 8, 1941 he walked upstairs to the bathroom, where he fell dead from an acute heart failure.

*Case 2. Ruptured aneurysm of the abdominal aorta with arteriosclerotic cardiac vascular disease.*

*History.* Mr. J. O., aged 67, white, a widower, was referred to Temple University Hospital October 12, 1939 for abdominal pain, distention, and shock. The patient, a retired business man, had been under the care of a cardiologist for fourteen years. He had had a coronary thrombosis in 1938, for which he was hospitalized for nine weeks, but was in his usual health until September 25, 1939, when he went to a physician's office to have a colonic irrigation, and having returned home by trolley, generalized abdominal pain suddenly developed, for which he was put to bed and an ice cap applied over the abdomen. Partial relief followed for three days but some abdominal distress and distention with eructation of gas continued. On October 9, 1939 a second sudden attack of acute abdominal pain developed at the level of the umbilicus and became generalized. Two days later a similar attack occurred, for which a physician was called and found him in shock. The patient was then transferred to Temple University Hospital.



*Examination.* On percussion the heart was found enlarged to the left. The first sounds faint and audible at the apex; the second sound was not heard. The abdomen was enlarged and distended, with dependent dullness.

*Operation.* The day after admission the abdomen was opened under spinal anesthesia and the abdominal cavity explored by the hand through a vertical rectus incision; about 200 cc. of thick dark liquid blood was removed. A globular pulsating enlargement the size of a grapefruit was felt over the lower half of the abdominal aorta, from which a wide cone-shaped expansion of elevated peritoneum extended upward over the proximal abdominal aorta, due apparently to the elevation of the peritoneum from the underlying aorta and aneurysmal sac by hemorrhage. Occlusion of the abdominal aorta was considered but it was concluded to be too hazardous to open the distended posterior layer of abdominal peritoneum and expose the aorta in the presence of a leaking aneurysm. The abdominal incision was closed in layers by interrupted fine wire sutures. The left external iliac artery and vein were then exposed extraperitoneally through an oblique lower left quadrant, muscle-splitting incision, the vessels divided and ligated below, and the cardiac ends united end to end with fine arterial silk interrupted and continuous sutures. The end of the artery was atheromatous and a satisfactory junction was made only after the artery had been trimmed back twice. The inguinal wound was united in layers with interrupted wire sutures without drainage. The patient passed through the operation in fair condition, and two days later was relatively comfortable. The left leg was warm but without arterial pulsation. The veins of both legs were distended and there was a loud bruit heard and felt over the area of anastomosis, and a slight cyanosis and mottling of the left thigh was apparent. The abdomen was soft and the general condition satisfactory.

*Course.* Three days after operation the patient was somewhat irrational, the left leg and toes were warm, and the abdomen was not distended; the temperature, pulse and respiration were normal and the heart sounds were of a "gallop" type.

A week after operation the hemoglobin was 9.5 Gm.; the red blood cells, 3,520,000. On October 13 the hemoglobin was 7.5 Gm., the erythrocytes 3,010,000, color index 176, leukocytes 15,950, polymorphonuclears 76, nonfilaments 9, filaments 67. There were coarse and finely granular casts in the urine with a moderate amount of occult blood, and evidence of albumen. Eighteen days after the operation (October 31, 1939) the patient was discharged to an infirmary, where he continued as a bedfast patient in fairly good condition for two months. He was then permitted out of bed, when he died suddenly from recurrent rupture of the aneurysm. Following his improvement after the vascular anastomosis it was perhaps an error not to have attempted a reinforcement of the aneurysm, as by cellophane or stainless steel gauze, before permitting him to become ambulant.

#### COMMENT

Usually after the external iliac artery to vein anastomosis there is some post-operative weakness in the leg on the side of the ligation, which improves with use. In none has this prevented the patient from walking. The divided external iliac artery has usually shown areas of atheroma which narrow the lumen, so that a number of diseased arterial segments have often been trimmed away. This narrowing reduces the degree of decompression of the aneurysmal sac that it is desired to produce, and may render it necessary to perform the operation on the opposite side. After the external iliac artery to vein anastomosis, a marked change in the aneurysm may be detected. Thus, in a patient with a large abdominal aneurysm and thin abdominal walls the effect of the anastomosis was very evident. By palpation before operation the aneurysm was continuously tense, with exacerbation during systole. After the operation the sac became relaxed and flaccid between and less tense during systoles. From this it would



seem that the circulation in the vaso vasorum should be improved by the operation.

While rupture has occurred after these anastomoses, it has been less frequent than in aneurysms without the surgical decompression.

Other operations also used for aneurysms of the abdominal aorta are ligation, cellophane fibrosis and electrothermic coagulation. Ligation of the aorta, of necessity below the level of the renal arteries, for abdominal aortic aneurysms has been repeatedly tried but only 6 patients have survived even eleven months after the operation. Narrow ligatures applied to the aorta soon ulcerate their way through the arterial wall, with fatal hemorrhage, as do also metallic bands or clamps used to partly or completely occlude the artery. Under ligatures made of a wide tape or strip of fascia or rubber bands, a slow necrotic process occurs but also with a tendency to eventual perforation.

Cellophane fibrosis produced by wrapping the artery, the aneurysm or both with 300 P.T. cellophane leads to a heavy deposit of fibroconnective tissue that gradually constricts the vessel and may reduce the size of the aneurysm. The cellophane wrapping should be covered by a layer of less reactive cellophane (300 P.U.T. 71) to protect the surrounding structures from fibrosis.

Perhaps the best result yet reported is De Takats' case 2. An 8 ply layer of cellophane was wrapped around the aorta proximal to the sac, which extended from just below the inferior mesenteric artery to the bifurcation of the iliaes. On the summit of this sac was a greenish, partly necrotic aortic plaque. An 8 ply layer was also wrapped around the anterior surface of the sac, which could not be encircled on account of adhesions to the spinal column. After the operation the patient had marked hypertension, but relief from abdominal pain, and returned to work. The cellophane created a hard, turret-shaped mass over the threatening perforation that could be well palpated through the abdomen. Fourteen months after operation the patient was working a full day. Two years after operation he died with an enlarging mass in the upper part of the abdomen.

With electric and roentgen guidance, Blakemore and Lord have evolved a precision technic for the deposit of coagula upon silver wire introduced into the aneurysmal sac. For selected saccular aneurysms that may be filled to the "brim" with firm coagula the method may be the best means yet devised, but used to slow or obstruct the blood flow in the aorta, the dangers from increases in wall pressure and from free coagula in the blood stream must be considered.

Our surgical experience with soft and very flexible stainless steel mesh has suggested the possible value of this medium for the reinforcement of the weakened aneurysmal wall.

In one patient we have used a reversed carotid-jugular anastomosis for an intracranial arteriovenous aneurysm. The patient, a man of 40 years, had an intracranial communication between the right carotid artery and cavernous sinus, characterized by loud bruit, marked exophthalmos and diminished vision of the right eye. Immediately after the anastomosis of the cephalic end of the divided carotid artery and the heart end of the divided jugular vein was com-

plete, the bruit ceased and the eye receded into its socket, and lost its congestion and vision. The circulation in the ocular fundus showed reversal. A year and a half later the man, apparently in good health, was doing heavy farm labor.

Theoretically the operation of carotid-jugular anastomosis as used for aneurysm seemed of possible value for congenital obstruction of the pulmonary artery with resulting well known cyanosis, inability to endure exertion, and tendency to pulmonary disease. Years ago I had occasion to try the operation on one patient—an emaciated girl of 7 years—with very advanced pulmonary tuberculosis, which led to her death a few weeks after the anastomosis. Obviously, the direct excision of the coarcted segment with end to end anastomosis has since proved to be both feasible and curative.

As the carotid-jugular anastomosis leads to a constant double oxygenation of a part of the circulating blood, it seemed worthy of trial in apparently hopeless cases of phthisis, with marked reduction in respiratory function. Three patients with bilateral advanced tuberculosis of the lungs, adjudged incurable, accepted a trial of the operation. Two of the patients were very emaciated Negroes—a race in which tuberculosis is notoriously virulent—and had been given an expectation of life of but two or three weeks. These two men lived several weeks after the operation without showing obvious change in the downward course of the disease. The third patient, a young white man with advanced bilateral pulmonary tuberculosis, had an average respiratory rate of 32 per minute during the week preceding the operation, which fell to an average of 22 after the operation. This suggested that the patient was being saved the exertion of over 14,000 respiratory movements daily through the double oxygenation of his blood. This man returned to the hospital apparently in excellent condition about eighteen months after the anastomosis. He had regained his normal weight, was free from cough or expectoration, but had developed a large pulsating swelling under the scar in his neck. Reoperation showed that a ball-shaped thrombus had formed on the lateral wall of the jugular vein below the anastomosis, evidently where the intima had been damaged by the provisional clamp placed at the time of the first operation. The thrombus impeded the flow of blood and evidently had led to the marked dilation of the very thin-walled jugular vein. This is the only venous enlargement we have seen after the direct arteriovenous anastomosis. The area of anastomosis was resected and the artery and vein ligated. Without the anastomosis the patient in a short time had a relapse of the tuberculosis, of which he died about six months later. This single experience suggested a possible use for the operation in certain otherwise hopeless stages of pulmonary tuberculosis, or in patients with inadequate oxygenating capacity from other causes. Except in the atherosclerotic, there seems to be little danger of hemiplegia following the carotid-jugular anastomosis in patients under 45 years of age, but larger vessels without this danger, as has been mentioned, are available.

## METHOD FOR THE TERMINAL VENO-VENOUS AND VENO-ARTERIOUS ANASTOMOSES\*

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The problem of blood vessel anastomosis which again has been brought to the fore, cannot be considered solved as yet. As a matter of fact, if the technique of the evertent sutures on two planes, which has altogether superseded the old method of so-called, "triangulation", and if the use of heparine has allowed us to make a remarkable step forward in the field of artero-arterial sutures, the same cannot be said of the veno-venous and veno-arterial anastomoses. An artery permits work to be carried out on a solid, resistant and resilient structure, while the delicate veins, often as thin as veil, have an extraordinary tendency to collapse and close. That is why, with regard to the latter, and in order to keep the vessel open and to be able to use a suitable plane of support during the suturing, a great need was felt for the employment of particular types of tubes (metallic and non-metallic; absorbent and non-absorbent) first proposed by Payr in 1904.

The interest aroused by the use of these tubes has increased since their introduction by Blakemore and Lord, who used for this, the almost inert material *vitallium* (Co., 65%; Cr., 30%; Mg., 5%). However, after an initial period of relative enthusiasm, some objections have been raised because it is expensive and difficult to obtain; because it does not appear to be as inert as it was thought to be at first; because surgeons are instinctively reluctant to leave an extraneous body in the tissue; and last but not least, because the anastomoses effected with vitallium tubes often remain permeable for only a short period of time (one month). The latter is a factor which is useful in cases where it is sufficient for the re-establishment of a valid collateral circulation (wounds in the limbs for instance), but certainly not so when a definitive permeability of the anastomosis is essential.

In order to eliminate these deficiencies, various proposals have recently been made concerning a modification of the technique (Learmonth, MacPherson) and the adoption of new types of tubes (J. Oudot, *et al.*). However, all such suggestions appeared in the literature only recently so that at this moment they cannot be readily evaluated.

The writers' concern is to contribute to the solution of this important problem by describing a technique, and recording the results obtained in the experimental employment of a tube (figs. 1-9) that differs from the Blakemore tube, and has been used in animals for termino-terminal, veno-venous and veno-arterial anastomoses (see Learmonth, MacPherson). The following features determined the use of the new tube: 1) it can be manufactured of any kind of material; rigid, a little resilient, non caustic or toxic (glass, bakelite, brass, alumi-

\* From the Surgical Clinic of the University, Rome.

num, stainless steel, etc.); 2) it has along its length a split which makes possible its easy removal from the vessels whenever desired, after the completion of the anastomoses.

Varying in length and diameter (from 6 x 3 to 15 x 6 mm.), tronco-conic in shape, having a dull point and an enlarged base (expansion of the base 2-3 mm.) with four equidistant holes (0.3-0.5 mm. in diameter) and a circular indenture in the middle of the almost cylindrical part (0.3 mm. wide and deep), the tube

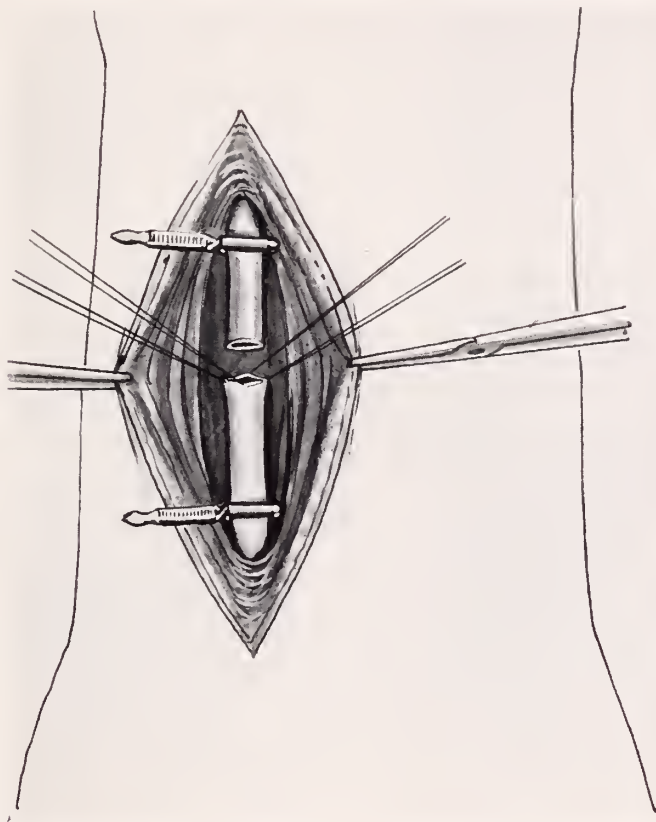


FIG. 1. Illustrating steps in the technique of vessel anastomosis with a removable tube, (see text).

under consideration (figs. 2-9), tested on animals for some months, has already proven its suitability in terms of the contemplated purpose.

The use of the tube is not difficult. Having applied the angiostate at the proper places, one of the 2 stumps to be anastomosed (usually the lower or most convenient one) is caught with a pincer. In the case of a veno-arterial anastomosis the vein is made to pass through the split in the tube. Four equidistant stitches (non-traumatic needles, 000000 silk) are made on the free border of the vein. When the apparatus is steadied by means of a pincer and the four threads are handled carefully with moderate tension, it is usually easy to "reflect" the vein



onto the tube, as illustrated in Figure 4. This done, the four threads with the above mentioned non-traumatic needles are passed through the corresponding four holes of the expanded vessel (base) one by one and knotted so that (figs. 4, 5) the reflected vein descending below the circular line (indenture) in the middle of the tube is afterwards kept steady. Then the other vessel stump is taken with delicate anatomic pincers (Stille-Crafoord) or by means of four threads, made to pass on the free ridge of the vessel (figs. 5, 6), and then made to descend delicately so as to join with the lower stump. Having thus achieved a perfect intima-intima contact, and in order to avoid retraction of the upper stump, the lower is fixed (fig. 6) by a knot using zero silk, delicately tightened at the height

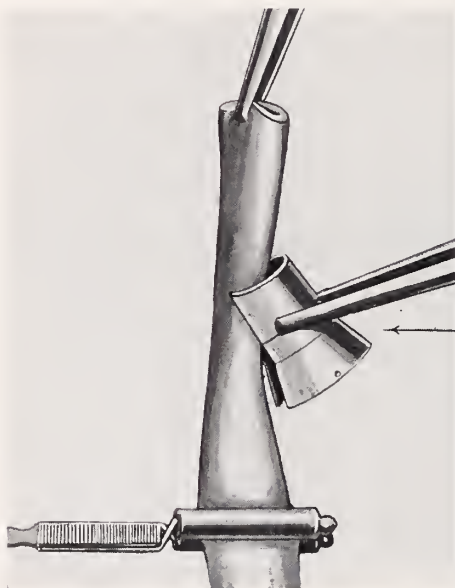


FIG. 2

FIG. 2. Illustrating steps in the technique of vessel anastomosis with a removable tube, (see text).

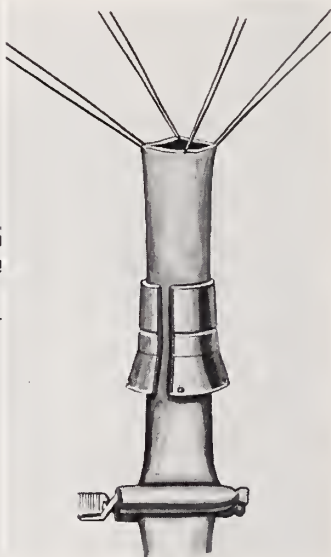


FIG. 3

FIG. 3. Illustrating steps in the technique of vessel anastomosis with a removable tube, (see text).

of the indenture which is visible through the reflected vein. When the two stumps have been joined, suturing is begun; non-traumatic needles, 000000 silk, interrupted sutures in U shape fashion are used, at  $\frac{1}{2}$  mm. distance from each other, in a double row (figs. 7, 8). Upon completion of the suture, the four sutures used to hold the lower stump to the expanded vessel are removed, together with the silk knot on the adventitia of the upper stump. Finally angiostats (always the one placed down-stream first and then the one placed up-stream) are also removed and results are observed. If the anastomosis is functioning properly and the suture holds without the need of additional stitches, the tube may be removed with delicate movements of a pincer, pulling it first downwards and then outwards (figs. 8, 9).

*Animal Experiments.* This type of anastomosis by means of the above described tube has been carried out by us 8 times to date, 6 veno-venous anastomoses, 2 arterio-venous anastomoses. Four were performed at the third intermediary of the external jugular vein; 2 at the third inferior of the iliac. The 2 veno-arterial anastomoses were performed between the artery and the femoral vein.

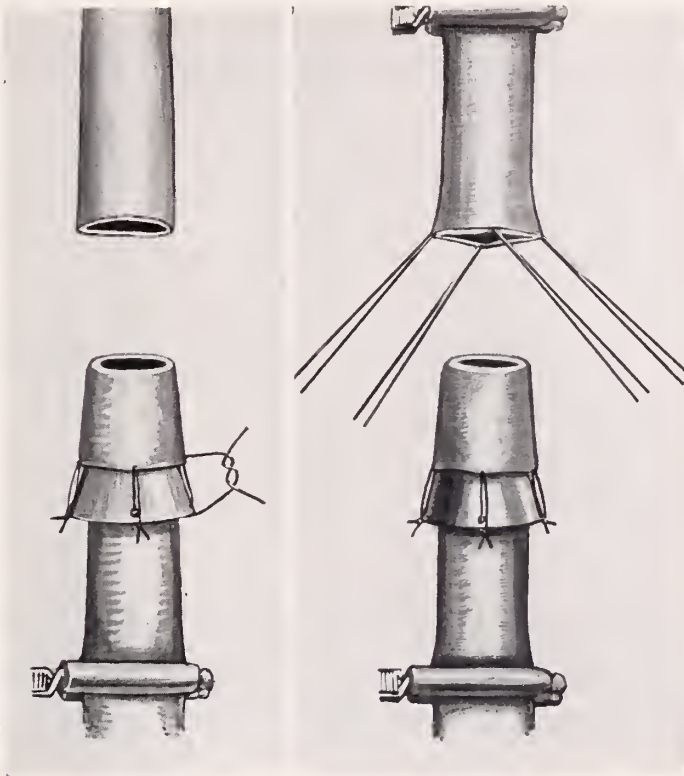


FIG. 4

FIG. 5

FIG. 4. Illustrating steps in the technique of vessel anastomosis with a removable tube, (see text).

FIG. 5. Illustrating steps in the technique of vessel anastomosis with a removable tube, (see text).

*Radiological Examination.* A rapid injection at a short distance from the suture of 10 cc. of 50% iodine solution—Joduron, enabled us to obtain very remarkable pictures (figs. 10, 11) and some important information as to the status of the vessels and the functioning of the anastomoses (stenosis, etc.) without having to remove the piece. We had to do so, however, in the last three cases.

*Microscopic Examination of the Anastomoses.* As expected we have constantly observed at the site of the anastomosis a circular enclosure, rather smooth, frequently adhering to the surrounding tissues, 5–12 mm. high, the diameter of

which in some cases appeared to be double the size of the anastomosed vessels (figs. 12, 13, 14).

*Microscopic Examination* of a portion of the joined vessels (3–4 mm. above and below the line of suture) disclosed intense hyperplasia of the adventitial connective tissue accompanied by striking vascular reaction (fig. 15). The media appeared to be invaded by connective tissue rich in vessels (for the most part newly formed) coming from the adventitia. The elastic fibres appeared to be well

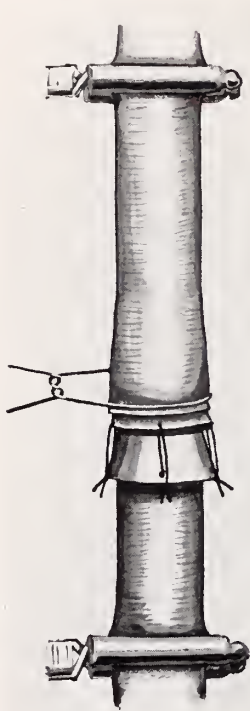


FIG. 6

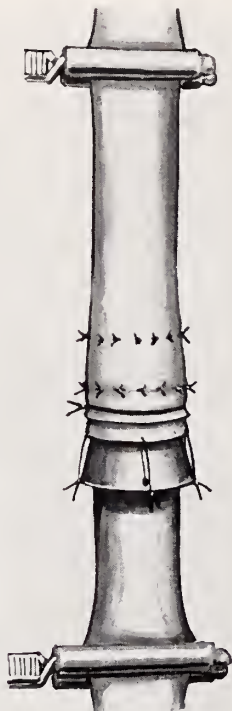


FIG. 7

FIG. 6. Illustrating steps in the technique of vessel anastomosis with a removable tube, (see text).

FIG. 7. Illustrating steps in the technique of vessel anastomosis with a removable tube, (see text).

preserved in the great majority of cases. At some points atrophy and degeneration are noticeable where the vascular coats have been compressed by the silk stitches. There was a non-uniform regional hyperplasia of the intima. The coalescence of the intima-intima (fig. 16—veno-venous suture) was perfect at some points; at others a layer of more or less abundant young connective tissue, rich in blood vessels (organization of small intermural thrombi) is interposed. At other points the interposed connective tissue has already overcome the phase of retraction and the two surfaces appear to be welded by a thin stratum

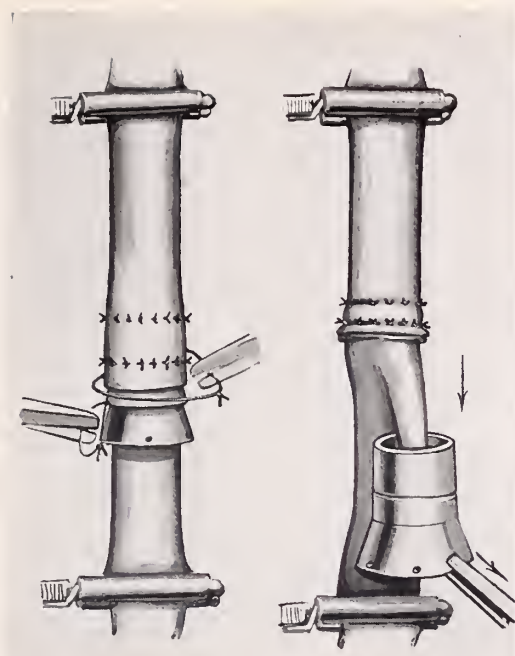


FIG. 8

FIG. 8. Illustrating steps in the technique of vessel anastomosis with a removable tube, (see text)

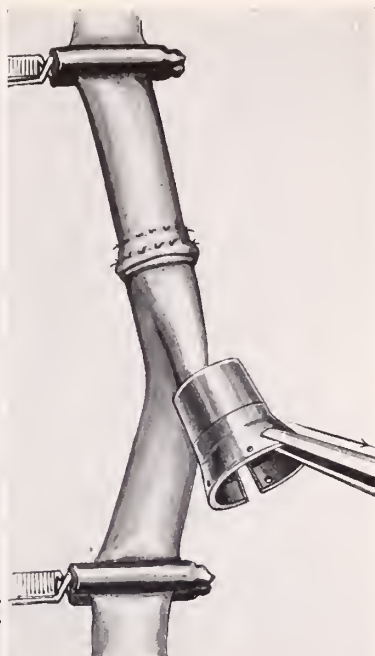


FIG. 9

FIG. 9. Illustrating steps in the technique of vessel anastomosis with a removable tube, (see text).



FIG. 10



FIG. 11

FIGS. 10 AND 11. Roentgenogram of the anastomosis performed with the removable tube.



of adult fibrocytes (figs. 17, 18—veno-venous suture), (figs. 19, 20—veno-arterial suture).

*Comment.* As far as the results are concerned it may be well to consider the veno-venous anastomoses first. There were no casualties, no instances of dehiscence or stenosis nor of aneurismal dilatation. Three cases of thrombosis appeared (2 jugular and 1 femoral) in animals controlled postoperatively, respectively on the 9th, 15th and 20th day after the carrying out of the anastomosis. In the remaining three animals one case of non-closed stenosis and two of previously fully performed anastomoses were observed respectively on the 22nd, 30th and 44th day. These were given adequate heparine treatment after the



FIG. 12

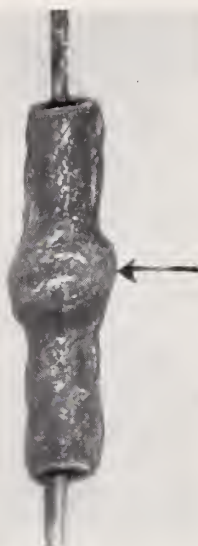


FIG. 13



FIG. 14

FIGS. 12, 13 AND 14. Drawings of gross specimens of the anastomosis performed with the removable tube.

operation and (in 2 cases) repeated novocaine infiltrations of the ganglia of the paravertebral sympathetics corresponding to the affected vessel.

Let us now consider the arterio-venous anastomoses: in spite of the protracted heparine treatment during and after the operation and the novocaine infiltration of the sympathetic corresponding to the affected vessel, a massive thrombosis and dehiscence of the suture took place in 10 days, in the first case; a very slight stenosis appeared in the second case, observed surgically on the 33rd day, where the artery was pouring into the vein (see for analogy: Leger) without causing manifest troubles.<sup>1</sup>

With scrupulous attention to asepsis, keeping the various stages in mind prior

<sup>1</sup> While this work was being delivered for printing, a very satisfactory result was obtained through the employment of the tube under reference performing in a dog the graftings of a vein (3 cm. long) in an artery (aorta) between renal and mesenteric.



FIG. 15

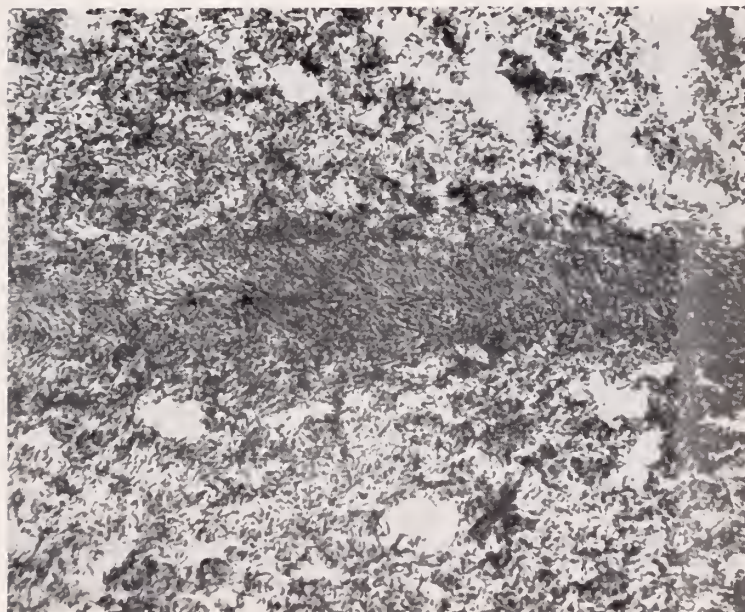


FIG. 16

FIGS. 15 AND 16. Photomicrograph, showing the histological structure at the point of the anastomosis (veno-venous, termino-terminal), performed with the removable tube.



to the surgical intervention, acting with the utmost care and judicious rapidity, ascertaining that the vessels to be anastomosed are of equal calibre, sparing the intima, endeavouring that the suture should not be too strained and that in

FIG. 17

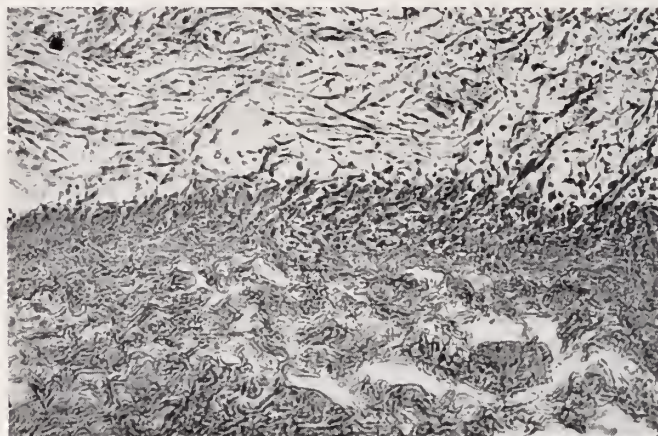


FIG. 18

FIGS. 17 AND 18. Photomicrographs, showing histological structure at the point of anastomosis, (see text).

between no fragments of adventitia should remain, dipping the needles and threads in vaseline oil shortly before their use, wetting the vasal stump frequently with anticoagulant solutions, removing the adventitia from the artery used in an anastomosis, effecting thorough hemostasis of the surrounding tissues,

prevention of pressure on the anastomosis, giving systematically and protractedly the heparine treatment after the operation, and making repeated novocaine infiltrations of the ganglia of the paravertebral sympathetic corresponding to the affected vessel . . . this is a series of provisions which the experience

FIG. 19

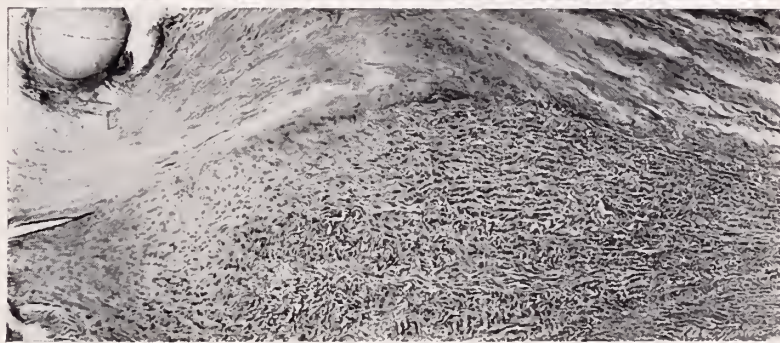


FIG. 20

FIGS. 19 AND 20. Photomicrograph, showing histological structure at the point of veno-arterious anastomosis.

acquired in the aforementioned tests makes us consider to be fundamental if we are to hope for a definitive or very long patent anastomosis.

#### SUMMARY

Having devised, constructed and experimented with a new type of tube for vascular surgery, with the special feature that it can be removed at the end of the operation, its use is proposed for termino-terminal veno-venous and veno-



arterial anastomoses (and also for the application of graftings of veins and arteries). The technique is described in detail including the post-surgical treatment, and the results obtained in a series of experimental tests are recorded.

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## PERIPHERAL ARTERIAL EMBOLISM\*

SAMUEL SILBERT, M.D.

During the past 20 years a better understanding of the physiopathologic events which follow peripheral arterial embolism has led to many changes in the treatment of this condition. It is now known that abrupt occlusion of a peripheral artery initiates spasm of all the blood vessels in the extremity, and that such spasm plays an important role in reducing the available blood supply. By the use of sympathetic nerve block and intravenous injections of papaverine much of this undesirable constriction of the arteries can be combatted. It is also understood that thrombosis proximal and distal to the actual embolism may shut off available collateral channels through which blood might flow to the distal part of the extremity, and that the outcome may be unfavorably influenced by the development of coincident venous thrombosis. The use of anti-coagulants to prevent such thrombosis is now recognized as essential to good treatment. It is known that ischemic tissues can be damaged by the use of heat, and in the modern management of peripheral arterial embolism such treatment is avoided. On the contrary, the beneficial effect of cooling ischemic tissues is recognized and employed. Finally the advantage of placing the extremity in a somewhat dependent position so that gravity will aid in restoration of circulation is appreciated. The present study was undertaken to determine to what degree these newer measures have been applied by the profession, and to establish whether or not their use has been reflected in demonstrable improvement in clinical results.

Recently Haimovici (1) analyzed the results of treatment in 330 instances of embolism of the peripheral arteries in 228 individuals. One hundred and forty three of these patients were ward cases at The Mount Sinai Hospital. I examined the majority of them as peripheral vascular consultant. Eighty-five were individuals seen by me in my private practice. The period covered was from 1928 to 1947 during which the newer methods of treatment have been proposed and employed. Twenty-nine of these cases were treated by embolectomy, one by arteriectomy and 300 were cared for by nonsurgical means. The latter group was divided into 115 untreated cases, 83 early treated cases and 102 late or poorly treated cases. The results of treatment are indicated in Table I.

*It will come as a surprise to many that more than half of all cases of peripheral arterial embolism recover without gangrene even when the condition remains untreated.* This fact must obviously be taken into consideration in evaluating methods of treatment. The degree of recovery of circulation in those patients who fail to develop gangrene varied a good deal. Perfect return of circulation with restoration of all peripheral pulses is rare. More frequently considerable impairment of circulation persists, resulting in such symptoms as intermittent

\* From the Peripheral Vascular Disease Clinic, The Mount Sinai Hospital, New York, N. Y.

claudication, rest pain and numbness. However, preservation of the extremity without gangrene offers a sharp and easily recognizable contrast to loss of the extremity because of gangrene, and thus serves as a rough measure of the efficiency of treatment.

One hundred and fifteen cases (Group A) are listed as having had no treatment. In many of these the condition remained unrecognized by the attending physician until gangrene developed. In others the symptoms were mild or evidences of rapid recovery were noted and special treatment was not used. The outcome in this group indicates the natural course of the disease, and serves as a basis of comparison against which to evaluate the various forms of treatment.

One hundred and two cases (Group B) are regarded as late or poorly treated cases. In the majority of them elevation of the extremity and the local application of heat were employed. Three out of every five cases seen in consultation practice have been treated in this manner. This is now generally recognized as harmful

TABLE I  
*Comparative results in treatment of peripheral arterial embolism*

GROUP	NUMBER OF CASES	TREATMENT	GANGRENE OR DEATH	RECOVERY WITHOUT GANGRENE	PER CENT OF FAVORABLE RESULTS
A	115	None	46	69	60
B	102	Late or poor	50	52	51
C	83	Early & good	24	59	71
D	29	Embolectomy	15	14	48

treatment, and the greater percentage of poor results may properly be attributed to this factor. In other cases treatment was delayed beyond 24 hours because the emergency nature of the condition was not appreciated. Failure to anticipate embolic complications in acute cardiac cases is often responsible for such delay.

Eighty-three cases (Group C) were treated within 12 hours of onset, and in these one or more of the newer methods of treatment were employed. These included moderate dependency of the extremities, local cooling, injections of papaverine, paravertebral sympathetic blocks with novocaine and the use of anticoagulants. Better results are noted in this group, with a higher percentage of favorable outcomes.

Twenty-nine cases (Group D) were subjected to embolectomy. The poorest percentage of recovery is noted in this group. Only when embolectomy is done in the first 12 hours after onset are better results noted. Thus, in 19 cases operated upon in this early period, 12 or 63% recovered without gangrene. Theoretically, embolectomy remains the treatment of choice whenever surgery is possible. If done early, and if in addition anticoagulants and other conservative measures are employed, it offers the best hope of restoration of good circulation to the extremity.

## SUMMARY

The outcome in 330 cases of peripheral arterial embolism under different forms of management is considered. Favorable results consisting of absence of gangrene and preservation of the extremity with complete or incomplete return of circulation was recorded in 60 per cent of untreated cases, 51 per cent of poorly treated cases, 71 per cent of early and well treated cases and 48 per cent of patients subjected to embolectomy. It is obvious from these figures that the fate of the extremity is largely decided by the pathological process, and the outcome up to now has not been strikingly influenced by the treatment employed. Harmful treatment due to ignorance of the physiopathologic events which follow peripheral embolism increases the number of poor results. Since only 83 of the total number are recorded as having received the benefit of antispasmodics and anti-coagulants, it is clear that the profession has not fully awakened to the possible benefits from these measures. The emergency nature of peripheral arterial embolism is still not generally appreciated and many patients are treated too little or too late. If prompt, aggressive and intelligent treatment is employed, utilizing the various therapeutic measures now available, the results obtained will probably show considerable improvement.

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RETROPERITONEAL SARCOMA (ADRENAL TUMOR?) WITH  
ACTIVE HEMORRHAGE. A SURGICAL EMERGENCY.  
RESECTION. TWENTY-SEVEN YEAR FOLLOW UP

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Dr. Berg's superb management of grave abdominal emergencies was compounded of knowledge, boldness and an exquisite technique. Those who were privileged to work with and learn from him, inevitably learned and then patterned their work on what they learned. The following case is an example of the stimulation derived from the master of surgical abdominal emergencies.

CASE REPORT

*History.* A woman, aged 30 years, entered The Mount Sinai Hospital in December, 1926, with the history that an appendectomy had been done two years before, for recurring abdominal cramps of several months' duration. After operation, she had felt well for a few months. She then began to experience epigastric fulness after meals, no matter how little she ate. There were no other symptoms. Six months before admission to the hospital she began to notice loss of weight which she believed amounted to fifteen pounds at the time of her admission to the hospital. Twenty-four hours prior to admission, violent cramp-like pain in the right lower quadrant began, continuing with increasing intensity. She vomited three times. Bowels moved with enemata. There were frequent chilly sensations and one well-defined chill shortly before admission. When the patient was seen one hour before entry into the hospital, a large cystic mass occupying the mesial and right side of the upper abdomen was noted. By the time the patient had entered the hospital, this mass had increased considerably in size.

*Examination.* On admission, the patient was found profoundly prostrated, pale, the respirations somewhat accelerated, and with wan and pinched facies. The general physical status was negative except for a few moist râles at the right apex. The abdomen exhibited a large, rounded, protruding mass, occupying the mid-portion and right side of the abdomen. The overlying skin was tensely stretched and the umbilicus pushed to the left and upwards. The mass was globular, about 20 cm., in its vertical and transverse diameters, smooth, tense, with a sense of fluctuation, tender, and fixed. The overlying abdominal musculature was rigid, but there was no generalized rigidity. On percussion, flatness existed only over the most prominent part of the mass. The white blood count was 21,200, with a differential of 80 per cent polymorphonuclear leucocytes.

*Operation.* Shortly after admission to the hospital, a free right upper rectus incision was made over the bulging portion of the mass. Upon opening the abdomen an enormous bluish tumor mass at once presented. The transverse colon was found to be displaced downwards and the mass appeared to lie in the transverse mesocolon. Over its upper surface, several greatly distended veins were noted. When the hand was passed into the abdominal cavity, the mass was felt to extend to the left as far as the spleen and to the right to the region of the right kidney, but the hand could not be passed around the mass. The deep limits were likewise ill-defined. Because of the firm consistency of the mass, enucleation of the clot and packing did not appear to be procedure that would be safe or most likely to control the hemorrhage. Accordingly, an attempt at removal was decided upon. The overlying transverse mesocolon was incised and bluntly separated. Additional thin layers of connective tissue overlying the mass were separated, until a plane of cleavage was found. It was then

clear that some type of capsule held the blood mass together. The overlying dilated veins were tied off and blunt dissection continued to the left in order to identify the colic media vessels. One branch had to be clamped and these vessels could then be retracted to the left. Further blunt dissection toward the left side of the mass established its retroperitoneal situation in juxtaposition to, but not derived from, the pancreas. Carrying the blunt dissection between pancreas and the mass, the latter could be partly lifted out of the abdomen for the first time. Making gentle traction on it, the right kidney was found to be drawn forwards. Sharp and blunt dissection was then continued over the right lateral aspect of the encapsulated blood mass. The third portion of the duodenum, closely related to the capsule, was dissected free and the pedicle could then be clearly identified. This was a flat mass of tumor tissue attached to the capsule of the upper pole of the right kidney but apparently not involving the kidney itself. The kidney appeared normal in size and consistency. It became now evident that the tumor might not be completely removed without sacrifice of the upper pole of the kidney. Accordingly, mattress sutures of chronic gut were passed through the upper portion of the kidney and tied, the kidney severed beyond these sutures, and the upper pole of kidney, together with the enormous blood clot mass was removed in one piece. A packing of gauze was introduced into the retroperitoneal space, surrounded by a strip of rubber dam; the remainder of the posterior peritoneum was sutured and the abdominal wound closed in layers around the drain.

*The specimen* was that of a spherical mass from 15 to 20 cm. in each diameter with a thin, confining membrane that held the blood clot together. Upon section, it consisted of recent and old blood clot and considerable fluid blood. Scattered throughout the blood clot were tumor masses of varying size, of grayish color, fragments of tumor tissue being freely distributed toward the periphery. The pedicle was a grayish tumor mass of uniform consistency. The attached portion of the kidney appeared normal. This was confirmed by the microscopic examination. The tumor tissue was reported as that of an angiosarcoma.

*Postoperative course.* The patient suffered considerable shock after operation, from which she recovered in three days. Pronounced abdominal distention was controlled by colon irrigations. The abdominal wound healed promptly after the removal of the drains. Two weeks after operation, when the patient appeared convalescent, there was a sudden onset of pain in the right chest and shoulder and physical examination revealed the existence of a pneumothorax. This was confirmed by x-ray. Two weeks later, pneumothorax had cleared up, its cause not having been determined, and the patient was discharged symptom-free.

Up to the present time, there have been no evidences of recurrence of the neoplasm. Deep x-ray therapy was employed over a period of several months. Two years after operation, the patient was admitted to the hospital for study to determine, if possible, whether or not recurrence or metastasis existed. X-ray examination of the chest and bones was negative. A gastrointestinal x-ray examination was negative. No evidence of lesion in the urinary tract was found by cystoscopy. Abdominal examination was and remains negative for the presence of a mass suggesting recurrence. The patient is in good health and has gained about twenty pounds since operation.\*

*Comment.* The following observations were made regarding the nature of the tumor: "Although some adrenal tumors present the microscopic characteristics of the organ from which they are derived, there are some others that can only be identified by their situation and characteristics. In this case a careful search was made in the effort to definitely place the neoplasm in the adrenal category. No trace of adrenal characteristics having been found, the conclusion that the tumor was probably derived from the adrenal can only be based on the clinical

\* The foregoing history of the case was read before a Stated Meeting of the New York Surgical Society, October 26, 1925.

picture. The latter, as given in this case report, is quite typical of an adrenal tumor with hemorrhage."

When the patient was seen in 1949, at the age of 56 years, she presented symptoms and signs of uterine fibromyoma. A hysterectomy was performed (by another surgeon) at which time no evidence of recurrence of the original tumor was found.

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# PRIMARY IDIOPATHIC SEGMENTAL HEMORRHAGIC INFARCTION OF THE GREATER OMENTUM\*

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In reaching the diagnosis of an "acute surgical abdomen" it should be borne in mind that one of the more unusual conditions which may be responsible for the symptoms is primary infarction of the greater omentum. A review of the literature reveals 16 authentic cases. Johnson (6) was first to record such an instance in 1932. Pines and Rabinowich (9) in 1940 reported six cases and in subsequent years additional cases were added to the literature (1, 2, 3, 4, 5, 6, 7, 8, 10). They have been recorded under a large assortment of terms, such as *idiopathic segmental infarction of greater omentum* (Pines and Rabinowich); *primary idiopathic segmental infarction of the greater omentum* [Totten (10)] and *hemorrhagic infarction of greater omentum* [Harris, Diller and Marcus (5)].

Etiology has been discussed by various authors. Totten (10) postulated that trauma produced a stretching of an omental vein which then resulted in thrombosis. The vascular congestion after a full meal added to increased intra-abdominal tension was thought to result in rupture rather than thrombosis. MacKenzie and Small (8) believe the mechanism is one of venous blockage, engorgement of veins, extravasation of blood into the tissues and an acute inflammatory infiltration. Harris and Diller (5) are inclined to the opinion that hypersthenic obese individuals are more likely to suffer this condition because of the increased gravitational pull of an extremely fatty omentum which results in rupture of a vessel.

The usual preoperative diagnosis is acute appendicitis. The condition seems to be more common in males. No case has yet been diagnosed correctly preoperatively. Most of the cases reported showed a hemorrhagic infarction in the terminal portion of the right or distal free border of the omentum although Cagney and Milroy (3) report a case of central infarction with recovery without excision. The mass in the omentum is usually red or purplish black in color and firm in consistency. No evidence of torsion was noted in any of the reported cases. This is an important point because primary torsion of the omentum is a distinct entity and is not included in this report.

## CASE REPORT

*History.* A. V. (\*575603), a Puerto Rican storekeeper, aged 28 years was admitted to The Mount Sinai Hospital at 3:15 P.M. on January 20, 1948 with a 24 hour history of abdominal pain. While recovering from an upper respiratory infection of five days duration he noted sharp stabbing pain in the right lower quadrant of the abdomen which became progressively worse. The patient had no chills, fever, diarrhea or constipation but did vomit once on the day prior to admission. Anorexia was present for twelve hours. On admission rectal temperature was 99.4°F.; pulse, 96, respirations, 20. The pharynx was injected. There was abdominal tenderness 3 inches to the right of the umbilicus. Rebound tenderness was present and consistently referred to McBurney's point. Associated muscle spasm of the

\* From the surgical service of Dr. John H. Garlock, The Mount Sinai Hospital, New York.



right rectus (mainly lower) was present. On rectal examination tenderness was elicited on the right side but no mass could be felt. The blood pressure was 130 systolic and 70 diastolic. At 4 P.M. the white blood count was 10,300 with 75% polys, 20% lymphos and 6% eosinophiles. Urine examination was negative. At 7:30 P.M. a second white blood count showed 13,600 with polys 70% (segs., 51, non-segs., 19), and lymphocytes 30%. The patient was observed for a period of four hours during which time the white blood count rose and the signs and symptoms persisted. A diagnosis of acute appendicitis was made and operation decided upon.

*Operation.* Anesthesia: cyclopropane ether inhalation. The abdomen was opened through a right rectus muscle splitting incision. There was some free colorless serous fluid present. The appendix was inspected and found to be normal. Palpation in the right upper quadrant revealed a mass. Therefore, the incision was extended upwards and the gall bladder and liver were visualized and found to be normal. The mass which had been palpated consisted of hemorrhagic infarcted omentum. The omentum was drawn together into a mass about 3 inches in diameter without any apparent torsion. It was adherent to the epiploic appendages in the region of the hepatic flexure. The involved omentum and adherent epiploic appendages were resected. The abdomen was closed in layers without drainage.

*The pathological report* (#96871): "Specimen consists of a large piece of omental tissue which is dark red, firm and nodular in areas and presents many adhesions between omental surfaces. Cut section reveals a firm, dark red tissue with mottled areas of yellow. There are many blood clots scattered about between the fatty lobules. A vessel is found with a very small lumen which is apparently not thrombosed. Also received is a small piece of epiploic appendage. Microscopic examination showed segment of fat tissue (omentum) showing hemorrhagic infarction and smaller fragment (epiploic appendage) showing acute inflammation."

*The postoperative course* was uneventful, the wound healed by primary union and the patient was discharged on the ninth postoperative day. At the last follow-up visit on October 6, 1949, the patient was symptom free and in good condition. On the day following operation hemoglobin was taken and reported 16.6 grams or 115%. This was repeated the following day and reported 18.4 grams or 126%. Since the patient appeared to be well hydrated the readings must be considered as accurate and therefore abnormally high.

#### DISCUSSION

Primary idiopathic segmental hemorrhagic infarction of the Greater Omentum is the proper name for the disease under discussion since it includes all the criteria for a proper diagnosis. The greater frequency in the males, the age group of 30-60 years, the severity of the pain, the duration of symptoms for one to three days without evidence of diffuse peritonitis all may be of help in making an accurate preoperative diagnosis. The pain is probably due to thrombosis or engorgement of tissues since in the case reported by Cagney and Milroy a resection was not done and recovery without pain followed abdominal exploration. At the time of operation for a suspected acute appendix the omentum should be examined if the pathology in the appendix is not sufficient to explain the symptoms and signs. Resection of the omentum should be done since gangrene of the omentum may result. If the process subsides spontaneously adhesions between the omentum and other organs may then result and the patient may subsequently develop a torsion of the omentum or intestinal obstruction due to the adhesions. Although trauma may result in stretching of omental veins and vascular congestion does occur after a full meal the case histories of the patients reported do not bear out this relationship. Both obese and thin individuals are

subject to this condition. The finding of a polycythemia in the case herein reported is of interest and it is suggested that there may be a causal relation between the polycythemia and the development of omental infarction. This has not been previously reported.

#### SUMMARY AND CONCLUSION

1. The literature is reviewed and an additional case of primary idiopathic segmental hemorrhagic infarction of the greater omentum is presented.

2. The etiology is discussed and a possible relationship between polycythemia and this condition is suggested.

3. Exploration of the omentum should be included whenever the appendix does not show sufficient pathology to account for the clinical picture.

4. Resection of the omentum should be carried out both for cure and to prevent future complications.

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# RETRO-CECAL ABSCESS, A LATE SEQUEL OF ACUTE GANGRENOUS APPENDICITIS

## A CASE REPORT

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The following case is considered of sufficient interest to report.

*History.* D. D., a young American student aged 22 years, was admitted to the hospital of St. Raphael on October 9, 1935, complaining of severe abdominal pain of three days duration. He was nauseous, vomited repeatedly, and was constipated. On the day of admission he had chills and a rise in temperature. There was no sore throat, no cough and no urinary symptoms. His past and family histories were negative.

*Examination.* The patient was well developed and well nourished. He had complained of severe abdominal pain. His temperature was 104.6 F.; the pulse, 110; and respiration, 22. His blood pressure was 125 systolic and 74 diastolic. The throat, heart, and lungs were all normal. The abdomen was very tender and rigid over the right side, especially in the upper quadrant; no masses were felt and there were no fluid waves or shifting dullness. There was tenderness in the flank. The genitalia were normal. All reflexes were elicited and were within normal limits. The white blood count was 13,800 with 87 per cent polymorphonuclears. The urine was negative.

*Course.* The diagnosis was acute appendicitis, and an operation was performed.

A right para-rectus incision was made. The caecum was found under the liver and a retro-cecal gangrenous, perforated appendix was removed, the stump ligated, and the abdomen closed without drainage. The pathologic report was acute gangrenous perforated appendicitis.

The immediate post-operative course was uneventful and he was discharged on October 23, 1935; he remained well until December 26, 1949, when abdominal pain reappeared.

*Recurrence:* Three days before his readmission to the hospital (December 29, 1949) he became subject to pain in the umbilical region which settled in the right upper and lower quadrants. It was accompanied by nausea and constipation without vomiting. There were no urinary symptoms, no sore throat, no cough, no chills and no loss of weight or appetite. His temperature was 102.6 F.; pulse, 95; respirations, 30. The abdomen was markedly tender and rigid over the right quadrant; no masses were palpated, there was no shifting dullness, and no tenderness in the flank. The white blood count was 17,300 with 89 per cent polymorphonuclears. The urine was negative. The diagnosis at this time was perforated duodenal ulcer.

*Operation:* A right rectus incision excising the old scar was made. A few omental adhesions were found in the peritoneal cavity. The stomach, duodenum, and gall bladder were normal. The gastro-hepatic ligament was incised and the lesser sac exposed. The appendectomy site was exposed, the lateral peritoneal attachment of the caecum was incised, and the caecum dissected medially. A small foul colon abscess was found and inspection showed that the posterior wall of the caecum was covered with a grayish exudate which could be wiped away with gauze. There was no apparent perforation and no foreign body was present. The abscess was in the location of the previous appendicitis and there was no stump. A few particles of exudate were removed and a drain inserted through a stab wound.

The patient was given 300,000 units penicillin daily, streptomycin .5 Gm. every 6 hours,

aureomycin 250 Mg. every 6 hours and parenterally 3000 cc. 5 per cent glucose daily, and nothing by mouth for 48 hours. The discharge was moderate but never fecal and the wound healed completely at the end of two weeks when he was discharged. The pathologic report described the biopsied tissue as that of acute and chronic inflammation of fat.

#### COMMENT

It is felt that this retro-cecal abscess was a sequela of acute gangrenous perforated appendicitis occurring fourteen years after the original appendectomy.

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## SURGERY OF THE NEWBORN

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The failure to be familiar with the surgical conditions of early life leads to faulty diagnosis which, in turn, leads to poor treatment and results. The prompt diagnosis of surgical diseases is particularly important in the newborn period because they are emergencies and early surgical intervention offers these young patients their best chance of recovery. Unfortunately it is still the feeling of many surgeons and pediatricians alike that these conditions are incompatible with life and that it is useless to attempt operation. It does not seem to be very common knowledge that infants in the first forty-eight hours of life stand major surgical procedures far better than they do a week or so later.

The successful treatment of the surgical conditions of the newborn is dependent upon early operation, careful operative technic, and adequate preoperative and postoperative management. The surgeon must be accustomed to the gentle handling of the delicate tissues of the infant and to the use of small instruments and fine suture material; this is more important than the speed of operation. Rough handling of tissues, blood loss, and exposure to cold are very shocking to these infants. The anesthetist should be experienced in the use of anesthetic agents in infants. The assistance of experienced resident and nursing staffs is invaluable. Finally, the cooperation of the pediatrician is essential in the pre-operative and postoperative management.

An adequate fluid intake is of prime importance, and the newborn infant requires about 150 cc. per Kg. body weight per twenty-four hours. The parenteral administration of fluids is necessary in the care of surgical conditions of the newborn. Dehydration should be corrected before operation and parenteral fluids continued during and after operation until the oral administration is adequate. Fluids are best administered continuously by the intravenous route, and it is preferable to expose a vein at the ankle through a small incision and to tie a small needle, cannula or piece of plastic tubing in place. Infants are easily over-hydrated, and it is important to regulate the speed of administration of the intravenous fluids by a dropper arrangement in the intravenous set; 5 drops per minute will give an intake of 480 cc. in twenty-four hours. The type of fluid is also important because an excessive amount of isotonic solution of sodium chloride may result in edema of the body, the most serious being pulmonary edema; a mixture of two-thirds 5 per cent dextrose in distilled water and one-third 5 per cent dextrose in isotonic solution of sodium chloride will prevent this complication. Fluids administered by the subcutaneous route may be substituted, but are not as well absorbed as intravenous fluids. The intake of fluids should be increased to compensate for loss of body fluids by vomiting or gastric siphonage.

Blood is the most useful agent to combat operative shock and its use has done much to lower operative mortality. The surgical conditions to be discussed necessitate the administration of blood during operation and after operation if indicated. Type-specific or irradiated blood plasma is useful if shock is associated

with hemoconcentration. The amount of blood or plasma given is usually about 15 cc. per Kg. body weight. Determinations of hemoglobin content, hematocrit, red blood cell count, and plasma protein afford indices of hemodilution or hemoconcentration.

Infants in the newborn period may have a low concentration of prothrombin in the blood, and it is advisable to administer vitamin K in this period. Vitamins B and C are added to the intravenous fluids.

External heat during operations on newborn infants is important; this can be supplied by placing two hot water bags under an inverted tray used for sterilizing instruments, and covering the latter with warm blankets. Inhalation of oxygen supplied through a tent or cubicle is a useful measure after prolonged operations and for the treatment of any pulmonary complication. The temperature of the air within the tent or cubicle is maintained at a considerably higher level than is customary with oxygen tents. If the infant is premature, or if difficulty should be experienced in maintaining the body temperature at a normal level, the patient is placed in an incubator.

Vomiting or abdominal distention are controlled by the passage of a catheter or Levin tube into the stomach and maintenance of gastric siphonage (Wangenstein). The use of neostigmine methylsulfate, in doses of 3 to 5 minims of 1:4,000 solution, is helpful in postoperative adynamic ileus.

The uses of sulfonamides and antibiotics are well known. Penicillin is gradually replacing sulfonamide therapy because of the low incidence of toxic effects and its efficacy in surgical infections. Streptomycin and, more recently, aureomycin are of benefit in some infections. In consideration of these agents in the prevention and treatment of infections, the important role of adequate surgery must not be overlooked. These therapeutic aids are highly important but they have not replaced good surgery.

The essentials of preoperative and postoperative care (1) have been emphasized at the outset because they are indispensable in the treatment of surgical conditions of the newborn (fig. 1). The clinical and pathologic features and the treatment of these conditions will be discussed.

#### CONGENITAL ATRESIA OF THE ESOPHAGUS

Although atresia of the esophagus is not a common condition, over 500 cases have been reported in the literature. There is a variety of classifications of congenital anomalies of the esophagus, depending upon the presence or absence of an associated tracheo-esophageal fistula. In nearly all instances the upper portion of the esophagus ends as a blind pouch at the level of the first or second dorsal vertebra, and the lower segment of the esophagus enters the trachea just above its bifurcation, thus forming a tracheo-esophageal fistula (figs. 2 and 3). The condition is incompatible with life, as feedings cannot enter the stomach. Furthermore, feedings and accumulated secretions in the short upper pouch overflow into the trachea, and death soon results from aspiration pneumonia.

The symptoms of congenital atresia of the esophagus are noted soon after birth. The infant is seen to have an excess of saliva in the mouth with a resulting

choking and, usually, some cyanosis. When a feeding is given there is immediate regurgitation with aspiration of fluid into the air passages and an increase in the choking and cyanosis. Nurses in nurseries of the newborn should be taught to report these symptoms immediately and not to persist in further attempts at feeding. Examination of the chest often reveals moist rales in the lungs, usually in the right upper lobe.

Roentgenologic examination is of great aid in diagnosis. Under the fluoroscope, a small soft rubber catheter is passed down the esophagus as far as it will go. If an obstruction is met about 10 to 12 cm. from the mouth, the diagnosis of congenital atresia of the esophagus is confirmed. A roentgenogram with the



Fig. 1. Photograph of an infant in the early postoperative period following intestinal surgery, showing fluids administered parenterally through a small vein exposed at the ankle, gastric siphonage maintained by suction through bottles and oxygen let in by a vent in the cubicle. (The infant is exposed for the photograph).

catheter in place will then demonstrate the site of the obstruction. A small amount, no more than 2 cc., of iodized oil instilled into the catheter will clearly outline the upper esophageal pouch. Barium should never be used for this purpose because of the dangers of aspiration into the tracheobronchial tree. The roentgen examination should include the abdomen, for the presence of air in the stomach or intestines is indicative of a communication between the lower esophageal segment and the trachea (figs. 4-6).

Congenital anomalies of the esophagus are frequently associated with anomalies of other organs of the body, and some of these abnormalities in themselves may be incompatible with life unless corrected surgically. The most frequent of these anomalies have been abnormalities of the heart and urinary tract, and



imperforate anus. Unusual combinations of atresias of the esophagointestinal tract in the author's experience involved the esophagus, duodenum and rectum in one case (2).

The extent of the preoperative treatment depends upon the general condition of the patient and the pneumonic complications that may already have occurred. If the lungs are clear, the sooner operation is undertaken, the less likely is the chance of a pulmonary complication occurring to a degree sufficient to prevent operation. Ordinarily, not more than twenty-four hours will be sufficient time



FIG. 2

FIG. 2. Photograph of the thoracic organs at necropsy showing the site of the end-to-end anastomosis of the esophagus (arrow).

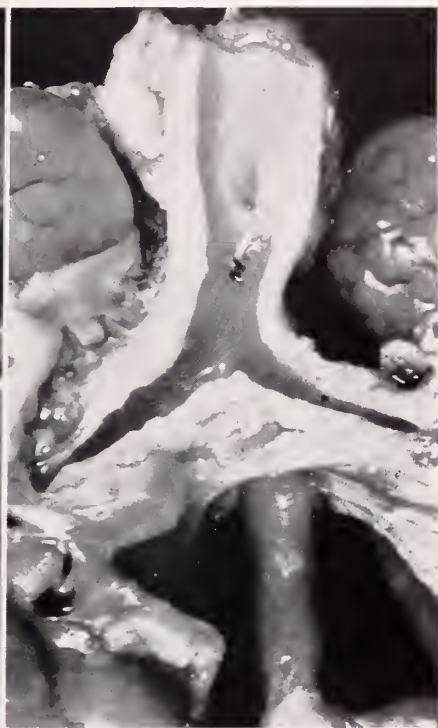


FIG. 3

FIG. 3. Photograph of the opened trachea at necropsy showing the site of the closed tracheo-esophageal fistula on the posterior wall.

to obtain the maximal beneficial response from preoperative treatment. Aspirations of secretions from the pharynx and the upper esophagus by a small, soft rubber catheter introduced into the pharynx should be done at frequent intervals in order to prevent the overflow of secretions into the trachea. Oxygen therapy should be started promptly. It is helpful to place the infant in the prone position and elevate the foot of the crib; frequent changes to alternate lateral positions are of importance in lessening the possibility of atelectasis of the lung. Other preoperative measures have been discussed.

Operation should be deferred in weak infants weighing less than 4 pounds, in



those infants in whom cyanosis persists after aspiration of mucus from the pharynx and after the use of oxygen therapy, and when fever is present. An extensive bilateral pneumonic consolidation is a definite contraindication to immediate operation. Penicillin should be employed in all cases. An early stage of pulmonary atelectasis usually responds to corrective measures.

Before discussing the plans of surgical treatment, mention should be made of the fact that gastrostomy alone is a procedure to be condemned because the gastrostomy feedings pass upward through the tracheoesophageal fistula into the lung, and the infant soon dies of aspiration pneumonia. Cyclopropane or



FIG. 4



FIG. 5

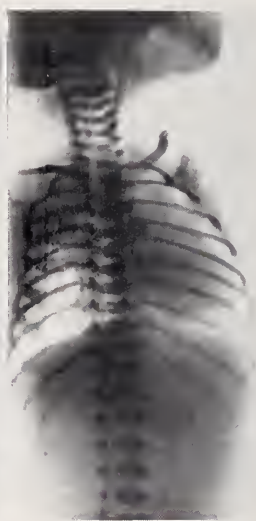


FIG. 6

FIG. 4. Roentgenogram of the chest and abdomen (barium administered) 1 day before admission showing a dilated upper pouch of esophagus, barium deposits in the lungs, and air in the intestines.

FIG. 5. Roentgenogram of the chest and abdomen (without the use of a contrast medium) on admission showing air in the gastrointestinal tract, and catheter in the esophagus obstructed at the superior thoracic aperture, and a consolidation of the right upper lobe in which a small amount of barium is visible.

FIG. 6. Roentgenogram of the chest and abdomen (without the use of contrast medium) on admission showing an absence of air in the gastrointestinal tract, a catheter in the esophagus obstructed at the level of the seventh cervical vertebra, and a consolidation of the upper third of the right lung.

ether and oxygen, administered through a small, snugly fitting mask, are the anesthetic agents. The operative exposure of the mediastinum is through a right upper retropleural approach. The operation of choice is division and ligation of the tracheoesophageal fistula and restoration of the continuity of the esophagus by anastomosis of the proximal and distal ends. The operation presents many technical difficulties due to the danger of penetration of the pleura, the small size of the distal segment of the esophagus, the distance between the two ends, and the structure of the esophageal wall. That these difficulties, however, can be overcome is shown by reports of successful anastomoses (6, 11, 18). A gas-

trostomy, under local novocaine anesthesia, on the day before or the day following the anastomosis protects the suture line until oral feedings are started about the tenth postoperative day. In patients in whom the ends of the esophagus are too widely separated to warrant a primary anastomosis, a multiple-stage procedure is adopted (16). These indirect procedures have been variously modified, but in general follow the following plan: 1) extrapleural division and ligation of the tracheoesophageal fistula; 2) gastrostomy; 3) exteriorization of the upper esophageal pouch into the neck; and 4) construction of an anterior thoracic esophagus. The main disadvantage of the indirect plan is that it involves a number of surgical procedures, the most difficult of which is the construction of an anterior thoracic esophagus.

#### OBSTRUCTION OF THE SMALL INTESTINE

Although recoveries from intestinal obstruction in the newborn are no longer rarities, the mortality of this condition remains high. The factors in this high mortality are the following: 1) the poor condition of infants who are born prematurely or have serious associated congenital anomalies; 2) delayed operation due to late diagnosis; 3) inadequate supportive therapy; and 4) inadequate surgery. Fortunately, all of these causes, with the exception of the first, are being successfully eliminated. These factors will be considered in more detail. The preoperative and postoperative care of these infants has been discussed.

Early diagnosis should be emphasized, and depends upon a prompt evaluation of the clinical manifestations. Persistent vomiting is the primary symptom and is often noted during or after feeding on the first day of life; in some forms of intestinal obstruction vomiting may not start on the first day and may be intermittent. The vomitus is bile-stained, and, in obstructions below the duodenum changes to an intestinal character. The stools are usually smaller, drier in consistency, and grayish-green in color rather than the tarry appearance of normal meconium. However, in some instances the stools may resemble normal meconium very closely. By the second day of life, the stool of a normal infant on breast milk or formula shows milk curds. Abdominal distention may or may not be present, depending upon the level of obstruction and the length of time the infant has gone untreated. If the obstruction is in the duodenum, distention will be confined to the upper abdomen, or may be absent if the stomach has been emptied by repeated vomiting. If the obstruction is at a lower level, abdominal distention becomes marked and generalized. There may be visible and audible peristaltic movements. As the obstruction continues, the usual changes secondary to dehydration are noted. With infarction and perforation of the intestine these changes become more marked, and evidences of shock and/or peritonitis are present. Perforation of the intestine may occur as early as the first day of life (3).

Roentgen examination of the abdomen is of decisive aid in diagnosis. The large amounts of air swallowed by the infant distend the gastrointestinal tract proximal to the obstruction, in marked contrast to the absence of gas in the distal portion of the bowel; with more advanced obstructions fluid levels are

visible. For this reason, plain roentgenograms of the abdomen, in the prone and upright positions, will not only confirm the diagnosis of intestinal obstruction, but will provide an approximate localization of the site of obstruction (figs. 7-10). The administration of barium is unnecessary and dangerous; the barium may be aspirated into the lungs during vomiting, or may subsequently obstruct the intestine after operation.

Intestinal obstruction in the newborn is due to a variety of congenital abnormalities of the intestine representing its incomplete development in fetal life. These anomalies result in intestinal obstruction due to intrinsic or extrinsic lesions. The intrinsic abnormalities are atresias or stenoses of the intestine and



FIG. 7



FIG. 8

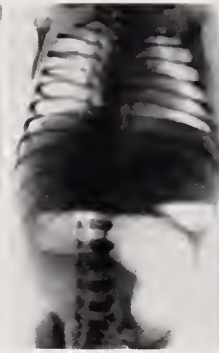


FIG. 9



FIG. 10

FIG. 7. Roentgenogram of the abdomen (without the use of a contrast medium) in an infant with atresia of the duodenum showing dilatation of the stomach and first part of the duodenum with an absence of air in the remainder of the intestinal tract.

FIG. 8. Roentgenogram of the abdomen (without the use of a contrast medium) in an infant with atresia of the jejunum showing dilatation of a loop of proximal jejunum with an absence of air in the remainder of the intestinal tract.

FIG. 9. Roentgenogram of the abdomen (without the use of a contrast medium) in the upright position in an infant with atresia of the jejunum showing air and fluid levels in the dilated loop of jejunum.

FIG. 10. Roentgenogram of the abdomen (without the use of a contrast medium) in an infant with atresia of the ileum showing several loops of distended small intestine with fluid levels; no air is seen in the large bowel; an ovoid mass with a calcific periphery is seen in the right lower quadrant.

meconium ileus, while the extrinsic obstructions are due to incomplete rotation and fixation of the intestine and defects in the mesentery. There are other very rare causes of intestinal obstruction, such as ring pancreas and congenital absence of nerve cells in the enteric nervous system.

Atresia of the intestine may be found in two forms. In the first—and less common variety—there is an internal diaphragm or veil which completely blocks the lumen. In the other form, the intestine ends as a blind sac and there is a discontinuity of the bowel. In the latter form, the proximal distended bowel is not attached to the distal collapsed portion, or else it is reconnected only by a thread-like fibrous band. In some cases there may be several atresias. Distal to the obstruction, the intestine is about 5 mm. in diameter and collapsed. Proximal to the obstruction, the intestine is greatly dilated and about 3 or 4 cm. in di-

ameter. Necrosis of the intestine with peritonitis may follow the formation of a volvulus of the distended blind end around the atretic cord, or perforation may be incidental to necrosis of the bowel secondary to occlusion of the arteries from overdistention of the intestine (fig. 11). Atresias may occur in any portion of the intestinal tract, but their most common sites are the duodenum, below the ampulla of Vater, the ileum, and the rectum. In some instances a diaphragm of tissue remaining within the intestinal lumen is incomplete; this is known as congenital stenosis of the intestine. These stenoses are much more common in the duodenum. The differentiation of atresia and stenosis is aided by Farber's test for the presence of cornified epithelial cells in the meconium (8).

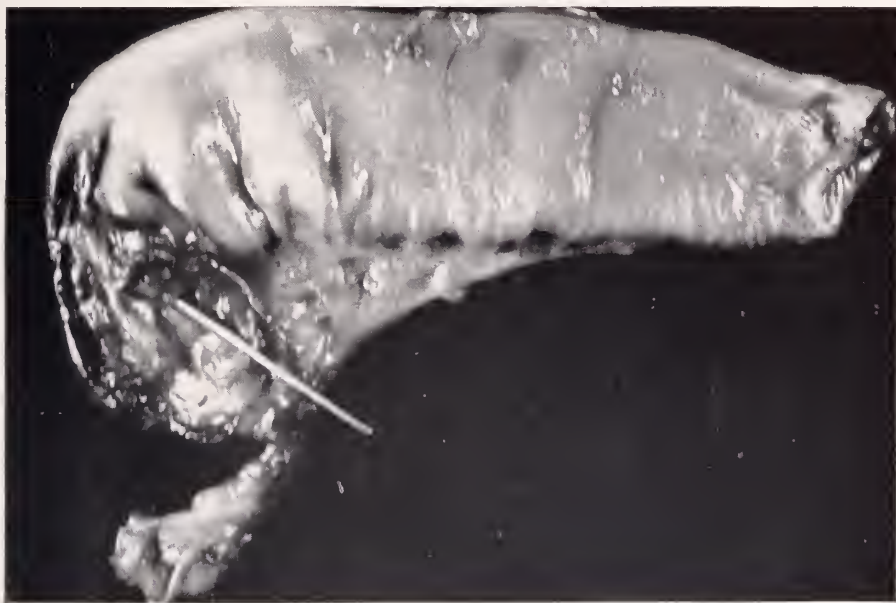


FIG. 11. Photograph of a resected segment of small intestine, showing the site of atresia of the ileum with the proximal and distal loops of intestine, and the area of necrosis with a probe passing through the site of perforation.

In the management of congenital atresias or stenoses of the intestine the principles of treatment previously stated are fundamental. The essential surgical treatment of congenital atresia or stenosis of the intestine is the establishment of a side-to-side anastomosis between the parts of the intestinal tract immediately above and below the site of obstruction. The uniformly bad results with enterostomy alone as an operative procedure in this condition should discourage any such operation. Infants in the newborn period do not tolerate the dehydration secondary to the loss of fluids and intestinal juices from an enterostomy. However, it is feasible to establish an enterostomy in the proximal loop as a procedure preliminary to, or in combination with, an anastomosis. The latter procedure is helpful in atresias of the ileum to control distention in an atonic bowel until the anastomosis functions; a useful expedient is to introduce the tip of the



enterostomy tube through the anastomosis into the colon, and through this to introduce saline solution. Side-to-side intestinal anastomoses in infants with congenital atresia of the intestine present problems in operative technic because of the disparity in size between the distended proximal loop and the collapsed and small distal loop. Since congenital atresias of the intestine are occasionally multiple, it is necessary to explore the intestine so as not to overlook additional atresias. If multiple atresias are present, the intestine below the lowermost atresia must be selected for the distal loop of the anastomosis. Patients with necrosis of the intestine present a still more difficult problem, because of the associated toxic state of the infants and the necessity for excision of the gangrenous part of the intestine. Operative management is still further complicated in the presence of peritonitis because anastomotic procedures are contraindicated in this condition. In one such infant in the author's experience, with congenital atresia of the ileum with gangrene, perforation and peritonitis, recovery followed a plan of staged operations consisting of obstructive resection, ileocolostomy and excision of the exteriorized ileum (3). Where large areas of the small intestine are side-tracked or excised, intestinal absorption may be considerably deranged. In the infant just mentioned 17 cm. of ileum were excised and an additional 23 cm. were side-tracked; severe diarrhea resulted and the feeding problem was a difficult one.

Congenital atresias of the colon are rarely encountered, but these malformations in the rectum and anus comprise an important group of these anomalies in the newborn, and will be discussed later.

A rare type of intrinsic intestinal obstruction is a condition known as meconium ileus. The clinical and roentgenologic manifestations of this lesion are indicative of an obstruction in the ileum. At operation, loops of jejunum are dilated. Almost the entire ileum is found on the right side of the abdomen, forming a mass of coiled intestines about the size of a fist. The ileum is contracted and thickened, and on palpation is filled with dense material. When opened, the ileum is found to be completely occupied by a cast of inspissated, pale green, firm, putty-like meconium extending to the ileocecal valve. The colon and rectum are small in calibre and collapsed, patent throughout, and empty except for a small amount of colorless, glairy, mucoid secretion. The physically altered meconium cannot be propelled through the bowel and is responsible for the intestinal obstruction. Postmortem examination of the pancreas in infants with meconium ileus reveals an obstructive lesion characterized by inspissation of secretions, dilatation of ducts, atrophy of acini, and fibrosis (9). A congenital stenosis of the main pancreatic duct has been demonstrated in 2 cases (13, 14). The relation of the pancreas to meconium ileus has been demonstrated clinically by analyses of the duodenal contents for tryptic activity showing a marked reduction or absence of this enzyme, and when the abnormal meconium was mixed with solutions of pancreatin it was quickly reduced to a semiliquid or liquid state (9). Therefore, the basic lesion in meconium ileus is thought to be cystic fibrosis of the pancreas and obstruction to the passage of pancreatic enzymes into the duodenum. The essential step in the operation for meconium ileus is the washing out of the inspissated meconium from the intestine through

an enterotomy (12). In addition to the postoperative measures for cases of intestinal obstruction, infants are given a protein milk formula fortified with glucose and casein hydrolysates, vitamins and pancreatin. The frequent development of pulmonary infections in infants who recover from operation suggests that the pancreatic lesion of meconium ileus is but one of the manifestations of a systemic disease.

Extrinsic obstructions of the intestine in the newborn are most commonly due to incomplete rotation and fixation of the intestine. In order to understand fully the condition of incomplete or malrotation of the intestine the basic embryologic facts of the development of the intestinal tract must be outlined (7).

In the three main subdivisions of the intestinal tract, the incidence of error in development is limited almost entirely to the midgut, that portion of the alimentary canal from the duodenum to the middle of the transverse colon. The reason for this greater incidence of error in the midgut is its somewhat complicated evolution in the fetus. The midgut is divided into two parts: the prearterial portion between the duodenum and the vitelline duct (or Meckel's diverticulum), and the postarterial portion between the vitelline duct and the middle of the transverse colon.

Prior to the tenth week of embryonic life, the midgut lies outside of the walls of the abdominal cavity within an umbilical sac. The aperture through which the umbilical sac communicates with the abdomen is small when compared with the size of the sac and its contents. The entrance of the contents of the sac into the abdominal cavity cannot proceed, therefore, *en masse*, but must slip back in a continuous movement (fig. 12).

At about the tenth week of fetal life, the movement toward the abdomen begins with the prearterial segment of the loop. The postarterial segment is held back in the sac by the cecum which forms a mass very large in comparison with the size of the colon (fig. 13).

The ventralization of the prearterial segment of the loop is followed by the cecum and what is left of the postarterial segment. Since these enter the abdomen above the coils of the prearterial segment it follows that the cecum, the appendix and the terminal ileum lie on the mass of coils of small gut. Here they are placed between the coils and the liver. As the midgut recedes into the abdominal cavity it rotates in a counter-clockwise direction, and the postarterial segment (the terminal ileum, cecum, ascending colon, and the transverse colon) lies wholly on the left side of the abdomen. As this anti-clockwise rotation continues, the cecum comes to lie in the superior part of the abdomen. Thus, in the eleventh week of fetal life, the cecum and proximal portion of the colon lies in the epigastrium. As the rotation continues, the cecum passes into the right upper quadrant and finally ends in the right lower quadrant of the abdomen. The colon as a whole is now in its proper relation to the coils of the small intestine, lying in the planes above them and on each side behind them so that this stage comes to an end, but it must be emphasized that although in their right places, the intestines are in no way attached to the dorsal wall except by their median mesentery (fig. 14).

After rotation of the midgut is completed, there is a final stage in the develop-

ment in which the cecum and ascending colon develop peritoneal attachments in the right side of the abdomen, and, the mesentery of the small intestine becomes attached to the posterior abdominal wall from the duodeno-jejunal junction obliquely downwards to the cecum.

There are two associated abnormalities resulting from incomplete rotation of the intestines. The first anomaly is related to arrest of development of the cecum in about the eleventh week of fetal life. The cecum is arrested in the epigastrium lying below the stomach, or it lies farther to the right side under the liver. In the former location, bands of peritoneum pass from the cecum to the right

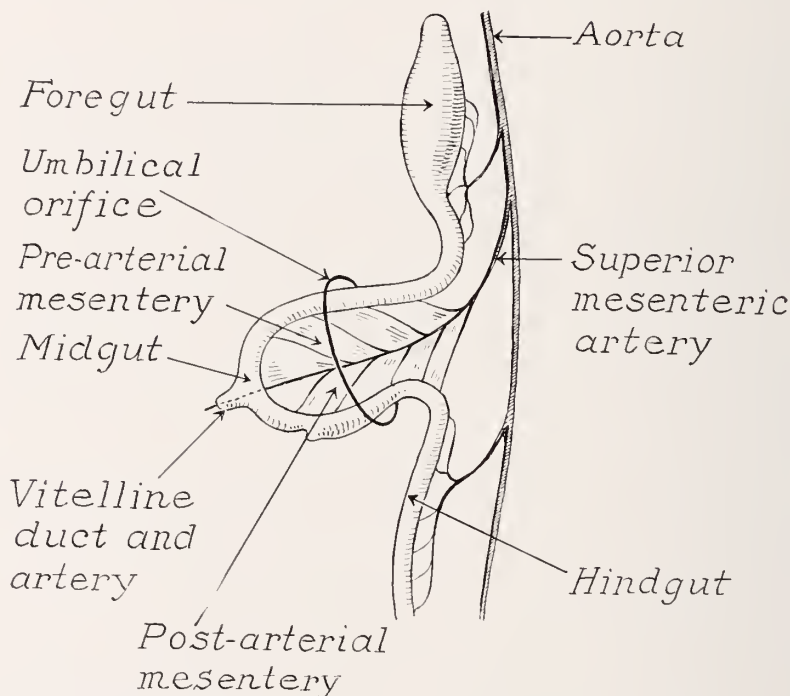


FIG. 12. Diagram representing conditions of primitive alimentary tract at fifth week of fetal life (lateral view). The foregut, midgut and hindgut are represented with blood supplies in the mesenteries. The midgut loop is large and is extended into the umbilical sac.

postero-lateral part of the abdominal walls and these bands pass across and obstruct the descending portion of the duodenum. In the latter position, the cecum itself lies on and obstructs the duodenum. The second anomaly is related to the arrest in development of the mesentery of the small intestine. In such cases, there is a small rudimentary mesentery below the origin of the superior mesenteric artery. Such a rudimentary attachment is conducive to a volvulus of the small intestine, starting with a coil of small intestine encircling the base of the mesentery. The end-result of these two anomalies is, therefore, an obstruction of the duodenum and a volvulus and infarction of the small intestine (fig. 15).

The symptoms and signs of malrotation of the intestine are related to the obstruction of the intestine. The earliest complaint is vomiting of bile-stained fluid. The obstruction is usually incomplete in the beginning so that stool is passed per rectum. Abdominal distention is a constant finding on examination. At first this is limited to the epigastrium and left upper quadrant since only the stomach and the first portion of the duodenum are dilated. As the lesion progresses the abdominal distention becomes more marked, and with advanced volvulus of the intestine, the distention becomes generalized. With necrosis of the volvulus, the picture of shock and/or peritonitis is present.

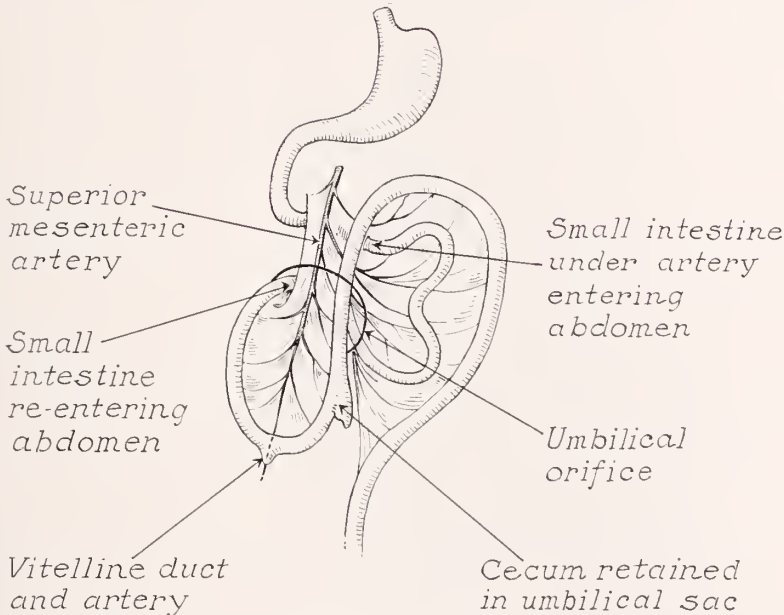


FIG. 13. Diagram representing conditions of the alimentary tract at the tenth week of fetal life (anterior view). The prearterial segment of the loop (the small intestine) has increased in length disproportionately to the postarterial segment. The small intestine is seen entering the abdomen on the right side of the superior mesenteric vessels and passing to the left side of the abdomen behind the mesenteric vessels. The cecum still lies in the sac.

As in other forms of intestinal obstruction, plain roentgen films of the abdomen are very informative. In the early stages, a dilated and gas-filled stomach and first portion of the duodenum are seen, and in the later stages, marked distention of the small intestine (fig. 16).

The knowledge of the mechanism of intestinal obstruction resulting from incomplete rotation of the intestine has a very practical significance in the operative treatment of this condition (15). After opening the abdominal cavity, it is necessary to exteriorize the loops of small intestine in order to visualize adequately the nature of the pathologic process. The cecum is found in the epigastrium or right upper quadrant, with obstruction of the duodenum either by bands or by the cecum itself. The posterior parietal peritoneum is incised



just to the right of the cecum, in this way exposing the descending portion of the duodenum. The cecum is displaced still further to the left side, thus relieving all obstruction of the duodenum. The duodeno-jejunal junction must now be visualized to expose the rudimentary mesentery of the small intestine below the origin of the superior mesenteric artery in order to determine the presence or absence of an associated volvulus of the small intestine. In advanced cases of volvulus with infarction, the blue dilated loops of small intestine are evident

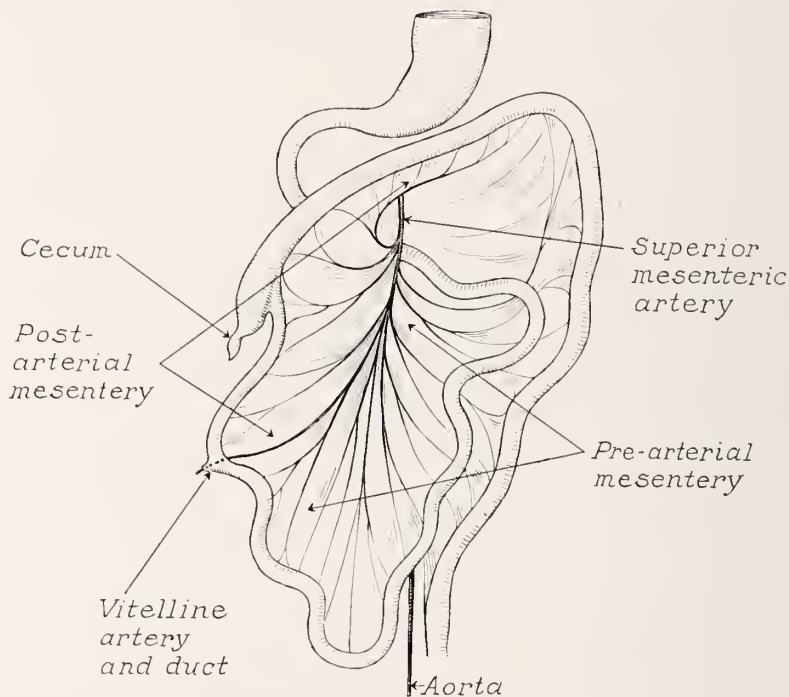


FIG. 14. Diagram illustrating conditions of the alimentary canal about the eleventh week of fetal life. The midgut loop has rotated on the axis of the superior mesenteric vessels through 270 degrees from its original sagittal plane. The cecum is now in contact with the posterior abdominal wall at the right loin. The essentials of the permanent disposition of the viscera has been attained.

immediately. If a volvulus is present, it takes place usually in a clockwise direction through one or more turns. The volvulus is reduced by turning the mass of intestines in a counter-clockwise fashion. When the volvulus is reduced, the normal color of the intestines is restored unless the volvulus has passed to its final stage with necrosis of the bowel. The above findings may be associated with an intrinsic obstruction of the duodenum, so that the exploration must not be discontinued at this point. This can be determined by passage of the gastric tube or catheter through the duodenum into the jejunum. If it meets no obstruction, the operator may be assured that an additional intrinsic obstruction of the duodenum is not present.

## CONGENITAL MALFORMATIONS OF THE ANUS AND RECTUM

Congenital malformations of the anus and rectum comprise an important group of anomalies in the newborn. These anomalies may involve the rectum, the anus, the urogenital organs, or combinations of these structures.

The rectal and anal anomalies and their associated malformations are inter-

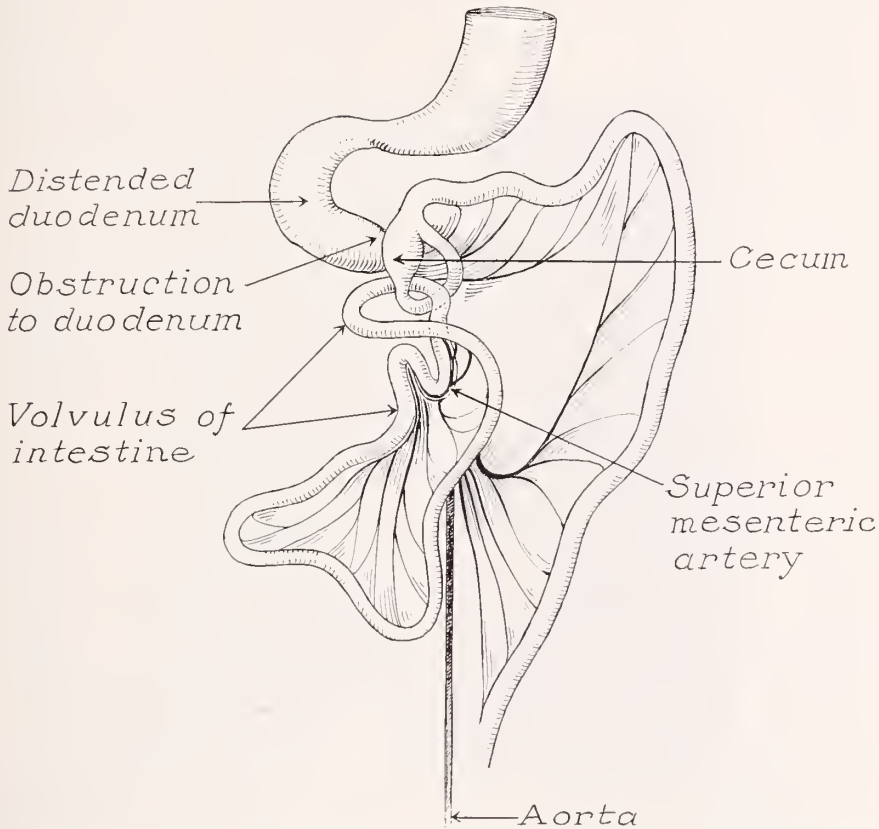


FIG. 15. Volvulus of the small intestine secondary to mal-rotation. The twist involves one complete turn from the original sagittal plane in a clockwise direction. The cecum lies in the epigastrium.

preted as arrests of development in the seventh or eighth week of fetal life. The external anal sphincter muscle which develops from mesodermal components is usually normal in all types of these malformations.

The most useful classification of congenital malformations of the rectum and anus is the following: Type I, a stenosis at the anus or at a point several centimeters above the anus; type II, an imperforate anus, the obstruction being membranous in character; type III, (the most common) an imperforate anus, the rectal pouch ending blindly some distance above the anus; type IV, a normal

anus and anal pouch, the rectal pouch ending blindly in the hollow of the sacrum.

Many infants with congenital anomalies of the rectum and anus have fistulous communications between the rectum and the genito-urinary organs or the perineum. In males, these may be rectovesical, rectourethral, or rectoperineal fistulas, whereas in females, these may be rectovesical, the more frequent rectovaginal (or recto-fossa navicularis), or rectoperineal fistulas. The incidence of these complicating fistulas was 28 to 68 per cent of reported cases in the literature (4)



FIG. 16. Roentgenogram of the abdomen (without the use of a contrast medium) in an infant with malrotation of the intestines showing dilatation of the stomach and first part of the duodenum with a very small amount of air in the remainder of the intestinal tract.

These fistulas occurred most frequently in patients with type III anomaly (figs. 17A, 17B, 17C, 17D).

Other congenital anomalies may be present, most commonly cardiac, urinary, or intestinal, and this anomaly may be the cause of death. The incidence of additional anomalies ranged from 28 to 68 per cent in various reports (4). These malformations are usually noted in the newborn period because meconium has not been passed, or meconium has come through an abnormal opening such as the urethra, vagina, or perineum. There may or may not be clinical evidence of intestinal obstruction, depending upon the duration of the obstruction (rarely manifest before forty-eight hours) and the presence or absence of an associated fistula.

The diagnosis of the type of malformation can be made by examination of the anal and urogenital organs. Type I is manifested by an anal or low rectal

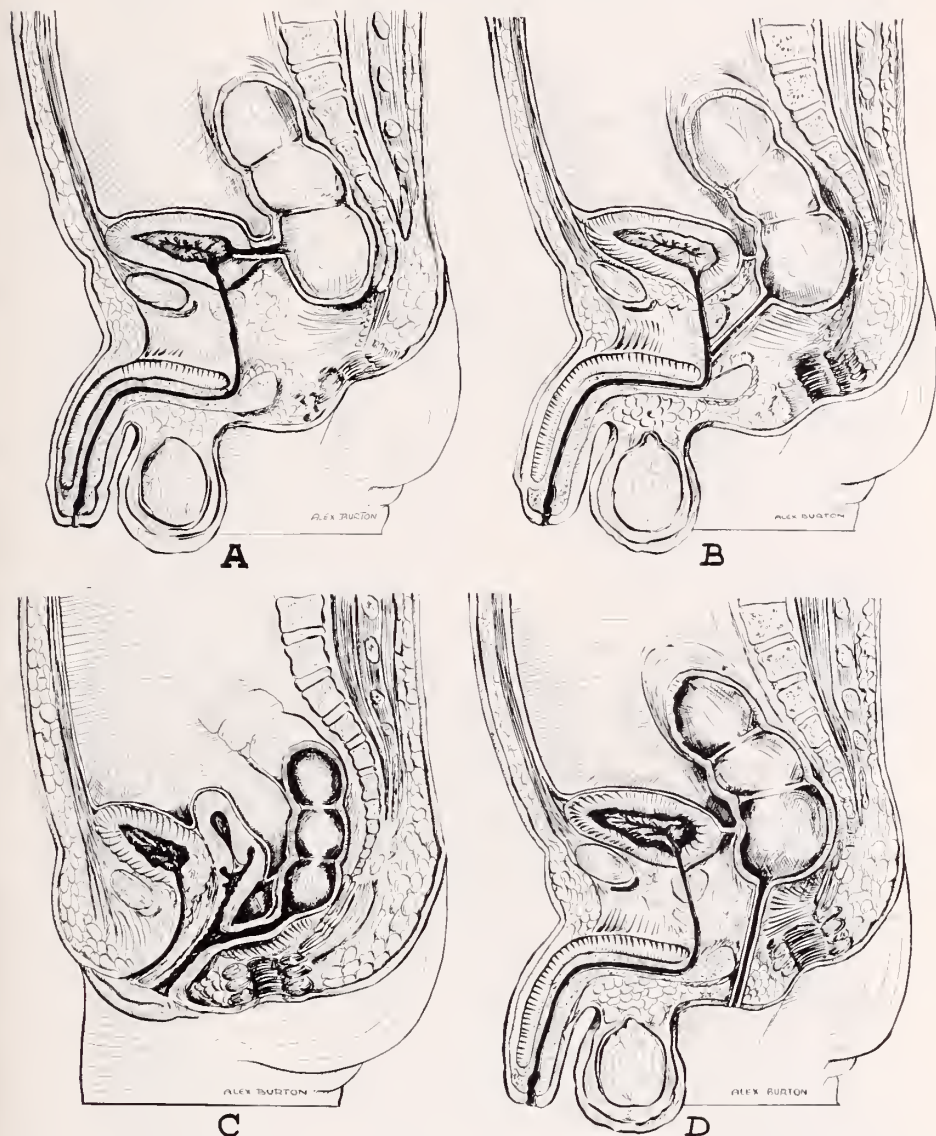


FIG. 17A. Sectional drawing of type III anorectal anomaly showing rectovesical fistula.

FIG. 17B. Sectional drawing of type III anorectal anomaly showing rectourethral fistula.

FIG. 17C. Sectional drawing of type III anorectal anomaly showing rectovaginal fistula.

FIG. 17D. Sectional drawing of type III anorectal anomaly showing rectoperineal fistula.

stenosis. A dark discoloration of an imperforate anus is noted in type II malformations. The anus is absent in type III anomalies, and a ridge or dimple with occasional pouching of the skin in this region is frequently seen. The open-



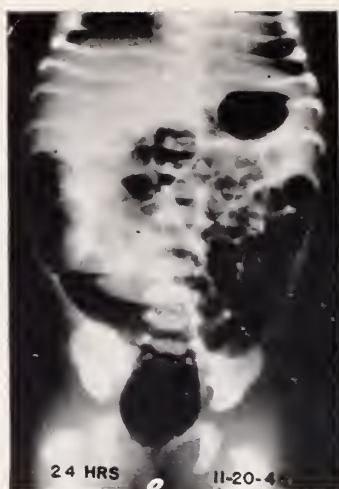


FIG. 18



FIG. 19

FIG. 18. Roentgenogram of the abdomen and pelvis in an infant with type III anorectal anomaly at the age of 24 hours, using the Wangenstein and Rice technic, showing the gastrointestinal tract filled with air and the rectal pouch clearly visualized in the pelvis.

FIG. 19. Roentgenogram of the abdomen and pelvis in an infant with type III anorectal anomaly at the age of 24 hours, using the Wangenstein and Rice technic in the lateral position, showing the gastrointestinal tract filled with air and the rectal pouch clearly visualized in the pelvis.



FIG. 20



FIG. 21

FIG. 20. Roentgenogram of the abdomen and pelvis in an infant with type III anorectal anomaly showing lipiodol injected into a rectoperineal fistula visualizing the fistula and the rectal pouch. The marker indicates the site of the imperforate anus.

FIG. 21. Roentgenogram of the abdomen and pelvis in an infant with type III anorectal anomaly, in the lateral position, showing lipiodol injected into a rectoperineal fistula visualizing the fistula and the rectal pouch. The marker indicates the site of the imperforate anus.

ing of a rectoperineal or low rectovaginal fistula is evident, but a rectourethral, rectovesical or high rectovaginal fistula will not be seen. Rectourinary fistulas will often show a mixture of meconium and urine, but inspissated meconium may not come through a narrow fistula. Type IV malformation is revealed by an obstruction in the ampulla of the rectum.

The accurate determination of the position of the rectal pouch has been aided by a special technic of roentgenologic examination (19) (figs. 18, 19). This consists of X-ray examination of the abdomen and pelvis with the infant suspended in a head-down position, and a radio-opaque marker at the site of the imperforate anus. The air in the colon will rise to the top of the rectal pouch, thereby revealing its proximity to the perineal skin. Roentgenograms in the



FIG. 22

FIG. 22. Roentgenogram of the abdomen and pelvis showing lipiodol injected into the distal loop of a sigmoidostomy visualizing the rectal pouch ending in the pelvis a great distance from the site of the imperforate anus.



FIG. 23

FIG. 23. Roentgenogram of the abdomen and pelvis showing lipiodol injected into the distal loop of a sigmoidostomy, in the lateral position, visualizing the rectal pouch ending in the pelvis a great distance from the site of the imperforate anus.

lateral and antero-posterior projections are taken. This method, however, may not be accurate in the first twenty-four hours of life because air has not reached the rectum. If the infant's condition is satisfactory, films during the second day will be more accurate. Another occasional source of error in the interpretation of the X-rays is the presence of a large amount of viscid meconium through which air cannot penetrate, even when films are taken during the second day.

Roentgen examination is also useful when there is an external fistula (figs. 20, 21). The injection of a radio-opaque material will outline the fistula and demonstrate its entrance into the rectum; this procedure will determine the size and length of the fistula and the location of the rectum. In patients who have had a colostomy the distal loop may be visualized by the same method to demonstrate fistulous communications and the position of the rectal pouch (figs. 22, 23).

The treatment of congenital malformations of the anus and rectum will vary

with the type of anomaly, and may involve a simple surgical procedure or a series of staged operations. The principles of preoperative and postoperative care are highly important and have been discussed earlier in the paper.

Stenosis of the anus and rectum is treated by repeated dilatations of the stricture. A membranous obstruction of an imperforate anus is cured by a cruciate incision of the membrane followed by repeated dilatations.

When the rectal pouch ends some distance above the imperforate anus, the type of operation depends upon the position of the rectal pouch and the possibility of reaching it by a perineal approach. In the latter procedure, with the infant in a lithotomy position, an anteroposterior incision is made to extend from the scrotum or vagina to the coccyx. The external anal sphincter is divided in the line of incision. Dissection is continued through the perineal fat, the levator ani muscle and the pelvic fascia, keeping the exposure close to the hollow of the sacrum to avoid the urethra and vagina. The rectum is brought down through the pelvic fascia, the levator ani and anal sphincter muscles to the perineal skin. These muscles and the skin are closed anterior and posterior to the rectum, the rectal pouch is opened, and the edges of the rectum are sutured to the surrounding skin.

Subsequent anal dilatations are very important. These are started during the second postoperative week by gentle insertion of the fifth finger. They should be conducted daily throughout the hospital stay, and continued by the parent until the anus feels and functions normally.

If the rectal pouch is 5 cm. or more above the anal pit the surgeon will experience great difficulty in mobilizing the rectum. In addition there may be so much tension on the suture line that necrosis and a poor result are obtained; later anal stricture and fecal incontinence may result. Under these conditions a primary colostomy is preferable. In such cases, too, if the perineal approach is unsuccessful it must be followed by a colostomy with a resultant high mortality. The sigmoid is chosen for the site of the colostomy, and it is important to perform a complete division of the colon to prevent the formation of inspissated stool in the distal limb of the sigmoid.

Further operative procedures are necessary in patients in whom a colostomy is performed (4). These are a reconstruction of the rectum through the perineum and closure of the colostomy. The completion of secondary procedures is advised before the child is 3 years old. Beyond that period the child with a colostomy becomes cognizant of the fact that he or she is not a normal individual, and one must consider the possibility of atrophy in a non-functioning anal sphincter.

The treatment of associated fistulas varies with the type of the fistula. Dilatation of fistulas should be rarely done and only if the child's condition is poor. Rectoperineal and low rectovaginal fistulas are easily repaired. The technic of the previously described perineal operation is employed. The fistula is completely excised and any internal opening is closed. The rectum is sufficiently mobilized to exteriorize the rectal end of the fistula, the opening of which is utilized for suture to the perianal skin. Attempts to close rectourinary and high

rectovaginal fistulas in infants are usually unsuccessful and should be deferred to a later age. A preliminary colostomy will aid in healing, and relief of the rectal obstruction may result in the spontaneous obliteration of such a fistula. Division of the fistula through an additional approach may be required. A preliminary suprapubic cystotomy will be necessary in the repair of large recto-urinary fistulas. The cystotomy will close with removal of the tube, and, finally, the colostomy is closed.

Primary abdominoperineal procedures have recently been introduced for cases in which the rectum ends at a great distance from the anal pit, with or without associated fistulas (17). This operative approach may become the operation of choice in these cases because it obviates the staged procedures necessitated by a colostomy.

#### OMPHALOCELE

Omphalocele, otherwise known as hernia into the umbilical cord, amniotic hernia or exomphalos, is an unusual congenital anomaly of the umbilical region in which there is a sac at the base of the umbilical cord consisting of thin, translucent, gelatinous-looking membrane. The sac, varying in size from a few centimeters to as much as 15 cm. in diameter, contains varying amounts of small intestine, colon and liver, either singly or in combination, and has a wide communication with the abdominal cavity. The neck of the sac is surrounded by skin, and the line of demarcation between skin and cord is clearly defined. The vessels of the cord course irregularly over the cephalic surface of the sac to meet together at its apex.

This condition resembles the status of the umbilical region in embryos from the sixth until the end of the ninth week of embryonic development, when the midgut, that portion of the alimentary canal from the duodenum to the middle of the transverse colon, lies outside of the walls of the abdominal cavity within an umbilical sac. The failure of the midgut to withdraw into the abdominal cavity has been considered to be due to a disturbance in the relationship of the growth process of the abdominal contents, whereby the abdominal viscera remains at the base of the umbilical cord because there is insufficient room for them to return to the abdominal cavity. This does not explain the presence of the liver within the sac which is considered to be related to a faulty development of the supraumbilical portion of the abdominal wall.

The wall of the sac rapidly undergoes changes. In the first twelve to twenty-four hours of life the wall is moist, translucent and pliable. After this time it becomes dry, opaque and friable, with a tendency to rupture. Such an accident is followed by evisceration and peritonitis (5). Even if unbroken, the membrane has a very low resistance to bacterial invasion.

Immediate operation is indicated for there is a definite relation between the time of operation and the operative mortality. Even infants with rupture of the sac have survived when operation was performed within the first twelve hours of life (5). Early operation is not only of advantage before infection has occurred, but because the stomach and intestines are not distended by food and



gas. The operation consists essentially of excision of the sac, replacement of its contents into the peritoneal cavity, and closure of the abdominal wall. The latter may be difficult because of the number of extruded viscera and the small size of the abdominal cavity. Under these circumstances a two-stage closure of the abdominal wall may be used; this consists of a primary closure of the subcutaneous fascia and skin, followed by a secondary closure of the abdominal wall one week later (15). The presence of liver within the omphalocele increases the difficulties of operation. Another type of procedure can be adopted in such cases. This consists of careful cleansing of the sac, incision and wide undermining of the surrounding skin, and closure of the cutaneous flaps over the sac, followed by secondary closure of the abdominal wall some months later (10).

#### CONGENITAL HERNIA OF THE DIAPHRAGM

Congenital hernia of the diaphragm is a serious lesion of the newborn which menaces the life of the individual. These hernias represent developmental defects of the diaphragm which may occur in various parts of that structure. The surgical problem in the newborn is concerned with those defects which occur in the posterolateral portion of the diaphragm. These openings vary considerably in extent and in amount of muscular tissue forming the posterior and lateral walls of the defect. The hernias are more common on the left side than on the right. There is a free communication between the pleural cavity on the affected side and the abdomen. There is rarely a hernial sac covering the involved abdominal viscera. The pleural cavity on the involved side is filled with a varying amount of the abdominal contents—small and large intestines, stomach, spleen or liver. There is a rudimentary attachment of the mesentery of the displaced viscera. The lung on that side is compressed, and the heart is shifted to the opposite side of the chest. The abdominal cavity is small in size as compared to the thorax.

The symptoms of congenital diaphragmatic hernia are usually noted at or soon after birth. Cyanosis and dyspnea of varying degree and duration are most common. Vomiting after feedings is occasionally seen. On physical examination, abnormal signs are found in the chest on the involved side—decrease of respiratory movement, dull or tympanitic percussion note, diminished or absent breath sounds, and occasionally intestinal gurgles. The heart is displaced to the opposite side of the chest. Examination of the abdomen reveals a scaphoid appearance and dullness on percussion.

Roentgenologic examination is of great aid in diagnosis (figs. 24, 25, 26). This should consist of plain films of the chest and abdomen in the anteroposterior and lateral prone and upright positions. The administration of barium is unnecessary and harmful; it may induce vomiting and complicates the surgical procedure. The involved side of the chest shows irregularities in density with a pattern suggestive of gas-filled loops of intestine, and the lung is compressed. The heart and mediastinal structures are displaced to the opposite side. The diaphragmatic shadow on the affected side is obscured by the herniated viscera which are continuous with those in the abdomen. In the usual type of diaphrag-

matic hernia in which a sac is absent, the viscera extend to the very top of the pleural cavity; when a sac is present this upward extension is usually more limited. The film of the abdomen reveals an absence of varying amounts of intestinal loops.

The risks of waiting are great, and operation should be undertaken as soon as the diagnosis is made. An additional advantage of operation in the newborn period is that the intestines are not yet distended.

The preoperative measures previously discussed are carried out, with special emphasis on the need for oxygen therapy.



FIG. 24



FIG. 25



FIG. 26

FIG. 24. Roentgenogram of the chest and abdomen (without the use of a contrast medium) in an infant with congenital hernia of the diaphragm showing gas-filled loops of intestine in the left pleural cavity, the heart and mediastinal structures displaced to the right side, and the stomach alone visualized in the abdomen.

FIG. 25. Roentgenogram of the chest and abdomen, 1 hour after ingestion of lipiodol, in an infant with congenital hernia of the diaphragm showing gas-filled loops of intestine, a few containing lipiodol, in the left pleural cavity, the heart and mediastinal structures displaced to the right side, and the stomach alone visualized in the abdomen.

FIG. 26. Roentgenogram of the chest and abdomen, after pneumoperitonium, in an infant with right-sided congenital hernia of the diaphragm showing the right pleural cavity occupied by the right lobe of the liver and gas-filled loops of intestine separated from the hernial sac by air, and the heart and mediastinal structures displaced to the left side.

The anesthetic of choice is cyclopropane administered with a small mask through a closed system allowing for the administration of positive pressure.

The operative approach is through the abdomen on the affected side. Intestinal loops are usually free of adhesions and can readily be withdrawn from the pleural cavity; this is facilitated by the rudimentary attachment of the mesentery. The removal of the viscera from the chest is facilitated by insertion of a catheter through the hernial opening to allow air to enter the pleural cavity. It is advisable to withdraw the herniated portion of the gastrointestinal tract in an orderly fashion, starting with the stomach, the small intestine, and finally the colon. Solid organs, such as the liver or spleen are left to the last. If a hernial sac is present, this is delivered after the emptying of its contents. The viscera

are allowed to lie on the abdominal wall, covered by warm compresses. The opening in the diaphragm is closed with a row of mattress sutures of silk which unite the diaphragmatic musculature, allowing for a free edge which can be used as an overlap. The catheter which had been inserted in the chest is allowed to remain in place until the last suture is ready to be tied. Positive pressure is applied through the anesthesia machine while the catheter is being aspirated; this maneuver will allow good expansion of the lung. The catheter is withdrawn when air can no longer be sucked out of the chest, and the last suture is then tied. The replacement of the viscera into the peritoneal cavity and the closure of the abdomen are often difficult because of the small size of the abdomen. The two-stage abdominal closure discussed in the treatment of omphalocele may be necessary (15).

The postoperative measures used in the surgery of intestinal obstruction are necessary in the first few days—parenteral fluids, with the addition of small doses of neostigmine methylsulfate in a 1:4,000 solution.

#### SUMMARY

The embryologic, pathologic, and clinical features, and the treatment of the surgical conditions of the newborn are reviewed. These congenital anomalies are atresia of the esophagus, atresia and stenosis of the small intestine, meconium ileus, malrotation of the intestines, malformations of the anus and rectum, omphalocele, and hernia of the diaphragm.

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## CONGENITAL ATRESIA OF THE BILE DUCTS

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It was not until John Thompson (1) in 1892 reported an analysis of fifty cases, and Holmes (2) in 1916 reported a study of one hundred cases, that congenital atresia of the bile ducts was recognized as a condition demanding surgical intervention, but the most significant contribution in this field was made by William Ladd (3) of Boston. His publications on this subject in the medical literature, and in collaboration with Robert E. Gross in their classical text, "Abdominal Surgery of Infancy and Childhood", led surgeons to begin to routinely explore these babies in the hope of finding a condition in which reconstructive surgery could be done.

However, in spite of the progress which has been made, congenital atresia of the bile ducts still presents an unpromising sphere for successful surgical therapy. In these cases, the extrahepatic ducts are either partially or completely represented by cords of fibrous tissue which have never cannalized into ducts. If surgical intervention is to be successful, the problem of how many of the extrahepatic ducts are cannalized, and the unknown problem of how many of the intrahepatic ducts are patent, must be resolved. In the absence of any patent extrahepatic ducts, we believe that the test operation we have devised of placing a catheter into the hilus of the liver, and establishing drainage with a biliary fistula is the operation of choice. This procedure demonstrates how many of the ducts within the liver structure are patent. After this has been determined, the Roux-Y operation can later be done. An opening is first made into the hilus of the liver at the point where the intrahepatic ducts emerge; and a medium sized number twelve or fourteen catheter placed one to one and a half inches into the substance of the liver where the right and left hepatic ducts are formed (fig. 1). The catheter is sutured into the hilus with silk, and brought out through a stab wound in the abdominal wall.

During the first few days, a clear water-like bile may be excreted through the catheter, but if the intrahepatic ducts are patent, within three or four days after surgery, there is a large elimination of bile. Several months later, after the jaundice has subsided, we feel justified in doing the Roux-Y procedure. A permanent cannula is inserted into the duct in the hilus of the liver. A loop of jejunum is transected, and the continuity of the gastrointestinal tract is reestablished through an end to side anastomosis. Using this method, we have been able to establish a free flow of bile in several patients, and they are still living and well. The percentage of such cases is small, but at the present time, surgical investigation is the only way in which it can be determined whether the liver has sufficient patent ducts to excrete enough bile compatible with life.

In two cases where the preliminary procedure had been done, the duodenum became adherent to the hilus of the liver. Eventually a spontaneous anastomosis

occurred between the duodenum and the liver. This was evident by the presence of a large amount of bile in the stools when the catheter was shut, in contrast to the acholic stools when bile drained through the open catheter. When the catheter was removed after several months, the biliary sinus closed, and the patient remained free of jaundice. The stools were normal in color with a sufficient amount of bile.

In cases where such a spontaneous anastomosis did not happen, a fistulous tract formed along the catheter from the liver to the skin. When these patients are reoperated, we utilize a portion of the tract for the anastomosis. The fistula is divided one-half or one inch from the hilus of the liver, and dilated. This method creates a larger opening for bile drainage. In our earlier experience, an anastomosis between the duodenum or the jejunum, and the stump of the tract, was made over a rubber catheter, and in recent years with the utilization of a vitallium tube.

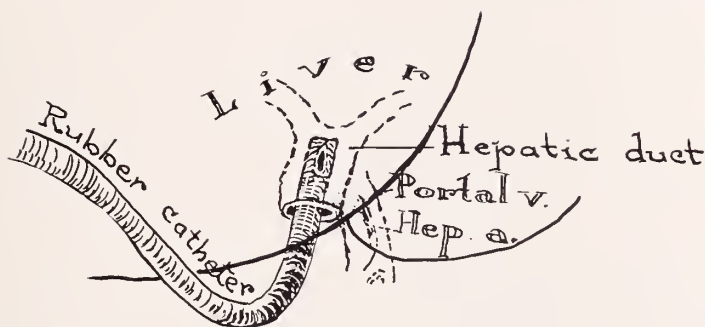


FIG. 1. The preliminary operation showing the rubber catheter placed into the hilus of the liver.

#### PATHOLOGY

The extrabiliary ducts are usually small cord-like structures of fibrous tissue possessing no lumen. Either the hepatic ducts, the common duct, the cystic duct, or the gallbladder may be atretic, but their relationship to the liver and the gastrohepatic ligament is normal. The extent of the obliteration varies, and the following pathology has been observed: (1) The gallbladder may be normal; but the cystic and common duct are obliterated, and a patent stump of the hepatic duct and the hilus are present. (2) The hepatic ducts may be atretic, while the gallbladder, cystic, and the lower part of the common duct are patent. (3) The lower part of the common duct may be represented by a cord-like structure; but the hepatic ducts, the cystic duct, and the gallbladder are patent, and the common duct is partially patent at the point of junction with the hepatic and cystic ducts. (4) There may be a complete obliteration of the hepatic, cystic and common ducts, with the gallbladder patent.

However, in a number of instances where the ducts appeared to be cord-like structures, we were able to establish a lumen by using a fine special soft silver needle, with a round blunted end. In one case, we were able to find the lumen

of the common duct. We discovered that part of the common duct was filled with inspissated bile and mucus. We thoroughly irrigated the ducts with saline solution up into the hilus of the liver. The opening which had been made in the common bile duct by the use of the needle was not closed. Within a short while, the infant had stools containing bile, the jaundice disappeared, and the child made a complete recovery.

Following this experience twenty-one years ago, we devised eyeglasses with a ten fold magnification, and adjustable focus. We also use fine flexible wire needles of various sizes, and fine pliable silver probes. We have found these instruments of great help in determining if we are dealing with a completely obliterated duct, or one containing inspissated bile and mucus plugs.

The gallbladder may be completely atretic; or if it is present, it may be small, and sometimes contains a clear mucoid substance. Occasionally it is quite large and distended, due to the presence of a secretion from its own mucosal glands. It may also be relatively normal, containing bile, which signifies that the hepatic ducts and the cystic duct are patent. However, in one case we operated, we found that the bile which was present in the gallbladder had been excreted from an accessory duct leading from the liver into the body of the gallbladder. Nevertheless, we do not believe that these small gallbladders should be connected with the intestinal tract. Such a procedure does not permit adequate biliary drainage from the liver.

The liver usually reveals a pronounced portal cirrhosis. It is from two to four times its normal size, depending on the duration of the obstruction. It is stained a dark-green color, and is nodular in character. In many cases, we found a greyish fibrous tissue between the nodular markings indicating an increased amount of interlobular connective tissue. Microscopically, there is a marked destruction of the liver tissue, and also evidence of regeneration. Ordinarily the ducts within the liver are not dilated. We have seen two cases, however, in which there was a partial obstruction from an anastomosis which had been made over a rubber catheter. When we operated these patients, we found there was marked dilatation within the intrahepatic ducts. This was determined by the good sized metal sounds which could be placed up into the hilus with ease.

In many cases in which the jaundice completely disappeared, the spleen was enlarged several years after operation, indicating a certain degree of portal obstruction.

#### PHYSICAL FINDINGS

Jaundice of a high degree is a pronounced symptom. While it may not be immediately observed at birth, within a few weeks it becomes evident. Once established, it becomes persistent, and deepens as the child grows older. The stools are clay colored at birth, and remain that way due to the complete absence of bile. These infants are usually well nourished in the first four or six weeks of life, but they may show nutritional deficiencies within the next two or three months. Most cases have normal blood findings. However in one patient the prothrombin time was prolonged, and surgery had to be postponed. The icteric

index usually ranged from 100 to 125. The abdomen is large due to the hepatomegaly, and a few may later show some ascites.

We rarely see these infants before the diagnosis has been established, and conditions such as icterus neonatorum, erythroblastosis fetalis, and congenital syphilis have been ruled out.

#### SURGICAL TECHNIQUE

In some of our earlier cases, where we used rubber catheters of various sizes for an anastomosis between the liver, or the hepatic ducts and the jejunum, we were able to establish permanent bile drainage. These patients are still living and well. In later years we began using the vitallium tube described by Pearse (4), (5) for choledochostomy, as well as in surgical procedures for congenital atresia. We found the vitallium tubes more satisfactory, but even some of these were expelled into the intestinal tract. As a consequence of this experience, we designed a vitallium tube with sharp prong-like projections at the upper end (fig. 2), and

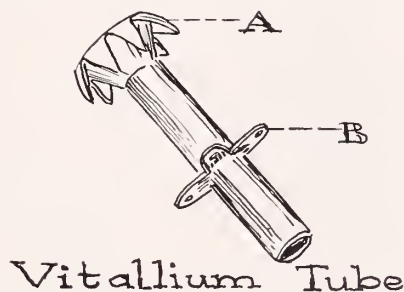


FIG. 2. A. Vitallium tube to be fastened within the liver substance. B. The metal arms lying between the hilus of and the closed purse string jejunum.

we are using this tube at the present time. When the tube is placed into the hilus of the liver, the prongs pierce the surrounding tissue so that it is almost impossible to dislodge the tube from its position. This has been successfully employed in several patients.

Following the preliminary operation where a biliary fistula is established, we use the one arm Roux-Y procedure as described by Cole, Ireneus and Reynolds (6). The drawings shown in this article have been taken from their paper.

The opening in the hilus of the liver created at the previous operation is dilated. The vitallium tube is inserted into this opening, and silk purse string sutures are used to fasten the tube (figs. 3, A and B). A loop of jejunum about 14 to 16 inches from the ligament of Treitz is divided. An end to side anastomosis with wax silk sutures is made between the proximal end of the divided bowel and the lower portion of the jejunum, approximately two feet away from the area of transection. An opening is made in the transverse mesocolon, and the arm of the jejunum to be anastomosed to the stump of the duct, or to the hilus of the liver, is placed through this opening so as to make it retrocolic. The opening in the mesocolon is sutured around the jejunum and its mesentery in order



to prevent a herniation of small bowel loops with possible obstruction (fig. 4). The open end of the divided jejunum is purse stringed with wax silk, (fig. 5-A). This purse string suture is tightened around the end of the vitallium tube emerging from the hilus of the liver (fig. 4-A). The metal arms of the tube are now located between the liver and the bowel. The bowel is now attached to the hilus of the liver with interrupted silk sutures. A small opening should be made about one to two inches from the end of the closed jejunum (fig. 4-B), and a fine forceps inserted to control the position of the vitallium tube. Interrupted sutures can then be placed in the jejunum which is to be attached to the hilus of the liver (fig. 4-B). Care must be taken to close this area carefully so as not to create tissue tension. The opening made in the jejunum by the forceps can then be closed. This procedure affords a double protection against the tube being dis-

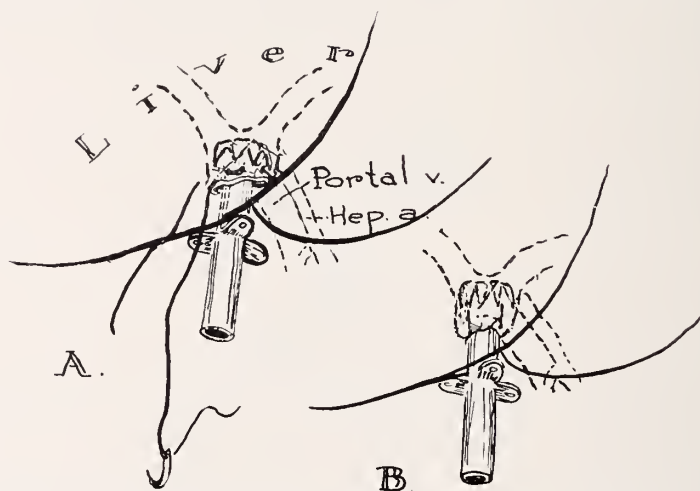


FIG. 3. Vitallium tube lying within the hilus of the liver, or within the common duct (A and B).

lodged; first, by the prongs fastened in the liver substance, and secondly, by the metal arms of the tube lying between the liver and the closed purse stringed jejunum. In some instances we included the arms of the vitallium tube in the closed jejunum, but found that this was not as satisfactory.

We have used the procedure suggested by Cole of making valves in the arm of the jejunum to prevent a reflux of the intestinal contents into the hilus of the liver. Usually four such valves, (figs. 6, A and B) are made. Interrupted sutures are used to fold the bowel wall into its lumen, thus forming a valve. Two small rubber drains are placed along the hilus of the liver, and brought out through a small stab incision, as a protection against possible bile leakage. These drains are ordinarily not removed until the eighth or tenth day.

#### ANALYSIS OF CASES AND RESULTS

In our earlier cases where an anastomosis had been made between the duodenum, and either the hilus of the liver, or the common or hepatic ducts, the

patients occasionally developed subsequent symptoms of cholangitis due to a reflux of intestinal contents into the biliary system. Each of these cases was re-operated, and the Roux-Y anastomosis described previously was done. All of these patients remained symptom free. The Roux-Y operation has been successful not only in children with congenital atresia of the bile ducts, but also in adults where we repaired the common duct.

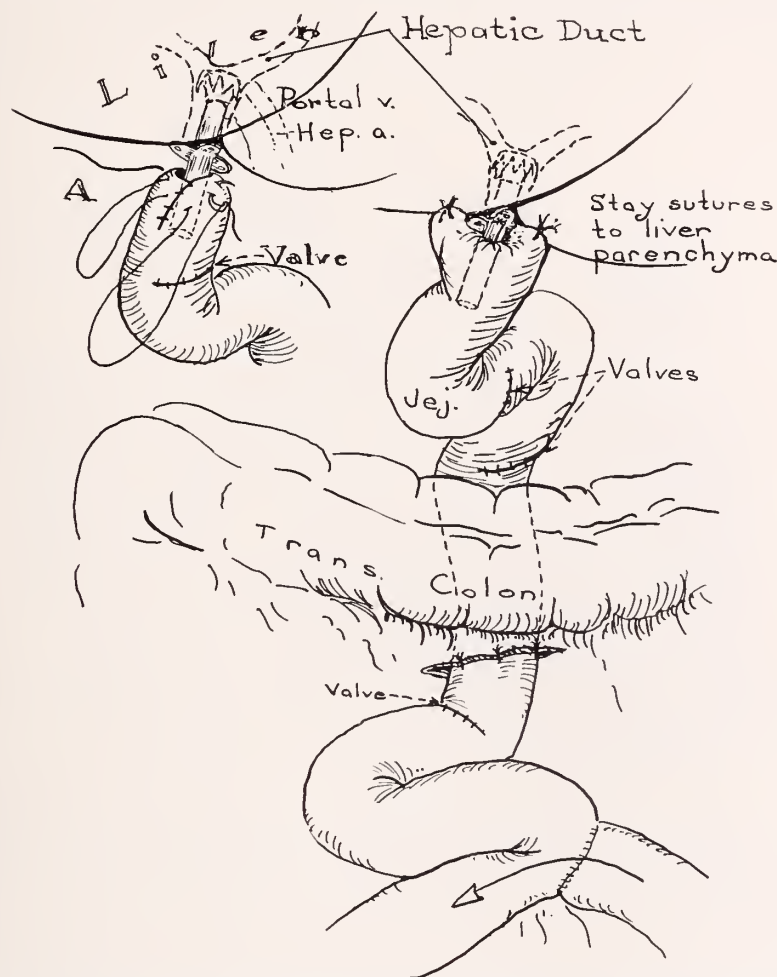


FIG. 4. The blind end of the jejunum has been passed through the mesocolon up to the liver. Inset A shows purse string of the jejunum around the vitallium tube below its arms. Stay sutures attach the blind end of jejunum to the capsule of the liver.

Of the forty-nine cases in our series where a surgical exploration was done, there were seventeen cases in which corrective surgery could be done. In this group there were seven patients with an obstruction of the biliary passages due to inspissated bile. Surgical treatment was instituted, and the obstructive plugs successfully dislodged by irrigation of the ductal system with saline. Six of these patients survived, and had no recurrence of symptoms. One later developed a

severe diabetes and died one year following surgery. The autopsy report showed a stone in the pancreatic duct. The relationship of the pancreatic duct stone to the diabetes is a matter of conjecture.

There were five patients where the hepatic duct was present, and a successful hepaticoduodenostomy was done. Two of these patients were subject to subsequent attacks of intermittent jaundice. In one of them, the severity of symptoms necessitated reoperation at which time a Roux-Y procedure was done.

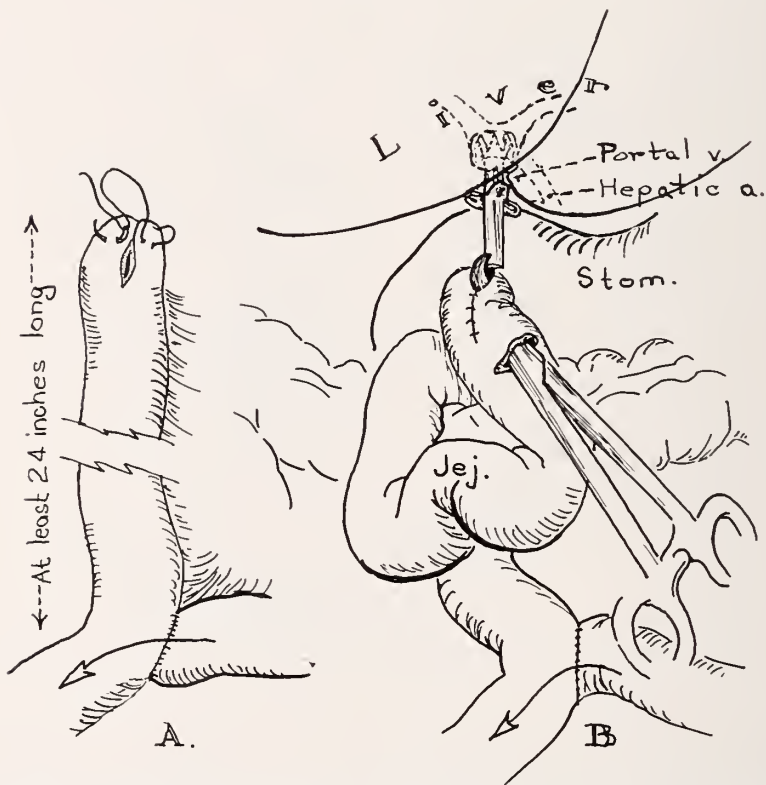


FIG. 5. Closed blind end of jejunum (A) with the purse string at least 24 inches from the end to side anastomosis of the jejunum, and (B) the vitallium tube in place. A forceps is introduced into the jejunum to draw the vitallium tube into the lumen of the bowel.

In five cases the hepatic ducts were obliterated, but we were able to create an artificial opening in the hilus of the liver. Two of these patients died, and three recovered. In one patient no further surgical therapy was necessary as a spontaneous anastomosis had occurred between the liver and the duodenum. In two cases, the preliminary operation was followed by an anastomosis between the fistula and the duodenum. One of these patients later developed symptoms of cholangitis. The last two patients in this group are of particular interest, and are described in detail below.

## CASE REPORT

*Case 1. History.* This white female child was seen by us for the first time at the age of seven weeks with a history of clay colored stools since birth, and increasing generalized jaundice.

*Physical examination* showed a distended abdomen with an enlarged liver, and a palpable spleen. The infant was operated on for the first time in May of 1932.

*Course:* Exploration revealed an atresia at the junction of the hepatic ducts, cirrhosis of the liver, and regional lymph adenitis. The common and hepatic bile ducts were explored. The hepatic duct was drained through a rubber catheter, which was led out through a stab incision. Several lymph glands and a piece of liver were removed for biopsy.

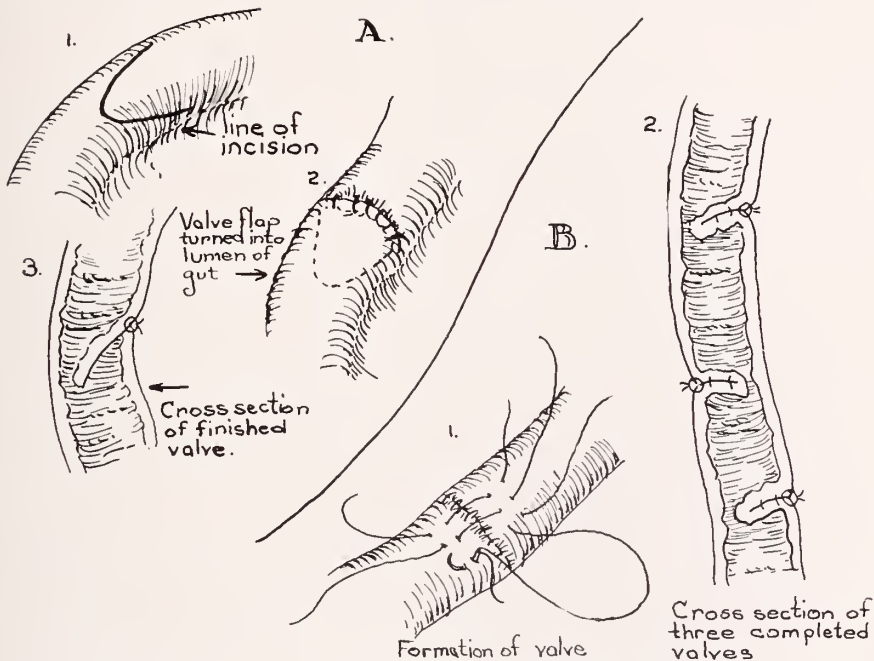


FIG. 6. Establishment of valves in the jejunum by the flap method (A) and by a fold in the lumen of the bowel (B). We prefer the latter procedure.

On the third postoperative day, bile started to drain through the tube. The child's condition improved steadily, and the patient was discharged twenty-two days after surgery. The catheter had been removed before the patient left the hospital. The icterus had subsided, and the stools contained bile. Apparently a spontaneous fistula had formed between the hepatic duet and the duodenum.

The child remained well for more than six years, but in August of 1938, the patient again became markedly jaundiced, and was readmitted to the hospital. On September 8, 1938, another external biliary fistula was established. The pathological findings at that time were adhesions of the small bowel to the abdominal wall, enlargement of the right lobe of the liver, and a small eirrhotic left lobe. The child made an uneventful recovery, and was discharged a month later with bile drainage from the sinus. She was readmitted in November of 1938, and an anastomosis established between the duodenum and the hilus of the liver.

In 1945 at the age of thirteen years, she entered the hospital with an episode of acute



poliomyelitis. She showed normal physical and mental development, and had led a normal social and academic life.

During the following years her progressive biliary cirrhosis became more apparent, and in September of 1948 she was admitted again for surgery. Due to bleeding manifestations, the operation was postponed until October of 1948 when a catheter was again placed into the hilus of the liver to relieve the biliary obstruction. In March of 1949, eighteen years after her first surgical procedure, she was operated again, and a Roux-Y procedure was done. This time a vitallium tube was used.

The postoperative period was complicated by several episodes of hematemesis, and persistent tarry stools, indicating a progressive cirrhosis of the liver. She left the hospital on the eighteenth postoperative day, but three weeks later was readmitted because of a severe hematemesis. Two days later she went into coma, and died following a convulsion. The autopsy findings were massive hemorrhage from esophageal varices, biliary cirrhosis with superimposed central necrosis and ascites, and congenital atresia of the extrahepatic bile ducts. There was a complete obliteration of the hepatic ducts which had formerly been present as a result of the advanced biliary cirrhosis.

*Case 2. History.* This white female infant was born at term on April 25, 1945 following a normal delivery, and was seen by us at the age of six weeks. Jaundice was present at birth, becoming progressively more severe, and the stools were acholic.

*Course:* An exploratory laparotomy was done on June 9, 1945 revealing an obliteration of the right and left hepatic ducts. The common duct was cord-like in character, and was only partially patent. A cavity, which appeared to be the right and left hepatic ducts, was found in the hilus of the liver. A number fourteen catheter was sutured there, and led out through a stab incision. The baby left the hospital with profuse bile drainage from the indwelling catheter on the eighteenth postoperative day following an uneventful recovery.

Four months later, on October 20, 1945, she was readmitted to the hospital for reconstructive surgery. At operation, on November 1, 1945, a biliary sinus was traced into the hilus of the liver. This was dissected one-half inch from the liver edge, and rubber catheters were inserted into the right and left hepatic ducts. An anastomosis was established between the liver and the duodenum. The postoperative convalescence was uneventful, and at the time of discharge from the hospital, she was free of jaundice.

However, eight weeks later, she vomited both catheters. She became mildly jaundiced, but did fairly well until May of 1946 when at the age of one year she was admitted to the hospital again because of increasing jaundice. Physical examination at this time revealed an enlarged liver extending down to the umbilicus, and a slightly enlarged spleen. Her blood findings were normal, and the icteric index was 36. A Roux-Y procedure was done on May 21, 1946. A vitallium tube of the older type was inserted into the hilus of the liver, and an anastomosis established between the jejunum and the liver. On June 1, 1946 the stools again contained bile, and the child was discharged on the nineteenth postoperative day.

During the following six months, she gained rapidly in weight, and learned to stand and walk. She remained free of jaundice, her stools were normal in color, and her selera were clear. Three months following this last operation the vitallium tube appeared in the stool, but apparently the artificial opening between the liver and the jejunum remained partially patent. Subsequent examination one year later found her moderately jaundiced, but the stools still contained considerable bile. The liver was enlarged, and approximately three fingers below the costal margin. It was of firm consistency, but not nodular. The tip of the spleen could be palpated two fingers below the costal margin. Yellowish-white patches had been apparent in her skin during the past month, and these were thought to be cholesterol deposits.

On January 20, 1948, she entered the hospital again, markedly jaundiced. Surgery on January 24, 1948 showed a marked cirrhosis of the liver. The junction of the liver with the jejunum was almost completely obstructed by scar tissue. There was no evidence of biliary

drainage. Another vitallium tube with prong-like projections was used to reanastomose the liver with the jejunum. Her convalescence was uneventful, and she was discharged in relatively good condition, with the exception of her jaundice which was just as severe as on admission.

During the following months, the child's course went progressively downhill. She remained jaundiced; the stools were acholic; there was a marked weight loss, and evidence of hypercholesterinemia and a secondary anemia. She was readmitted to the hospital in February of 1949, and death occurred a few days later. The autopsy findings were congenital atresia of the extrahepatic bile ducts with a complete obliteration of the hepatic ducts which had formerly been present due to the advanced biliary cirrhosis of the liver. There was also evidence of portal obstruction as indicated by the diffuse markings of hemorrhage in the bowel wall, but no esophageal varices were present.

#### SUMMARY AND CONCLUSIONS

1. While the number of permanent cures following surgical treatment for congenital atresia of the bile ducts is still small, some progress has been made in this field of surgery. All these patients should be subjected to surgical exploration. In Ladd's series, the number of cases amenable to correction was twenty per cent, and in our experience, it was approximately one-third of all patients who were explored.

2. By establishing a preliminary external biliary fistula, we were able to ascertain how many of the intrahepatic ducts were patent. Children in whom the jaundice does not disappear within three or four months after the preliminary operation may live for some time. However, the prognosis for eventual survival is poor because of the progressive biliary cirrhosis of the liver.

3. The utilization of the stump of the biliary fistula for subsequent anastomosis with the jejunum has been discussed. In one child the vitallium tube passed into the intestinal tract, but the anastomosis remained patent for more than one year. This was evident by the presence of bile in the stools.

4. The prognosis in cases where there is an obliteration of the bile ducts, due to inspissated bile or mucus, is excellent. Surgical relief is obtained by dilatation and irrigation of the ductal system.

5. The prognosis in cases of complete atresia of the extrabiliary system is unfavorable in spite of multiple operations, because of the progressive portal cirrhosis which eventually obliterates the remaining patent ducts. However, some of these patients may reach adolescence.

6. Reflux of the gastrointestinal contents into the biliary system has been successfully prevented by the use of the one arm Roux-Y operation.

7. All children with congenital atresia of the bile ducts deserve surgical therapy with careful exploration of the hilus of the liver.

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# ACUTE APPENDICITIS WITH MALROTATION OF THE CAECUM

## CASE REPORT

GERTRUDE FELSHIN, M.D.

Malrotation of the intestines is relatively uncommon and is explained by a developmental defect. This disturbance in the development of the intestinal tract



FIG. 1. Roentgenogram illustrating the fixation of the caecum in the right upper quadrant of the abdomen.

has been described fully in a previous paper (1) which drew attention to the importance of early recognition of this condition in intestinal obstruction.

The following case is one of acute appendicitis in a boy of 10 years who had a previously unrecognized and symptom-free malrotation of the intestines.



*History:* H.S. (Adm. # 531880), a boy aged 10 years, became acutely ill on March 10, 1945. He had severe pain in the right upper quadrant of the abdomen accompanied by vomiting of a bile colored fluid and a temperature elevation to 105°F. The pain persisted and he was admitted to The Mount Sinai Hospital on the following morning. A blood count disclosed hemoglobin, 76%; red blood cells, 3,800,000; white blood cells, 15,500 with segmented, 76%; mononuclears, 4%; lymphocytes, 14%; eosinophiles, 6%.

The vomiting and pain disappeared during that day but a board-like rigidity developed and the diagnosis most seriously considered was that of acute appendicitis. It was then decided to subject him to surgical intervention.

*Operation:* (Dr. H. Neuhof) The right rectus muscle was incised, but the caecum and ascending colon were not found in their usual position. The incision was then extended upward into the right upper quadrant, where a portion of the tip of the appendix was visualized. It projected forward out of the retroperitoneum just under the liver which had to be retracted to expose the appendix. This was dissected out and found to terminate at the caecum. The appendix was removed in the customary manner and was found to be acutely inflamed and gangrenous. The postoperative course was uneventful.

*Comment:* The accompanying x-ray photograph taken ten days post-operatively shows the caecum fixed in the right upper quadrant of the abdomen.

It is rather significant that a maternal uncle had a similar condition with a similar episode.

Because the pain, rigidity and rebound tenderness were localized to the right upper quadrant of the abdomen, the clinical course had at first suggested the remote probability of cholelithiasis. The presence of the acutely inflamed appendix at the liver border was subsequently explained by the malrotation of the caecum.

#### SUMMARY

1. A case of acute appendicitis with malrotated caecum is described.
2. The signs and symptoms were all referable to the right upper quadrant.
3. There was a similar case history in the family.

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# TECHNICAL PRINCIPLES IN MYOMECTOMY WITH SPECIAL REFERENCE TO HEMOSTASIS

I. C. RUBIN, M.D.

*In honoring Doctor A. A. Berg with this anniversary volume, we honor a great surgeon whose career began at the end of the last Century when bold intervention and technical expertness, based on knowledge of anatomy and pathology, were the surgeon's chief assets. Doctor Berg was endowed with these qualifications and more. Utilizing the newer knowledge of physiology and chemistry particularly as applied to the gastrointestinal tract, Doctor Berg was able to blaze the path for original surgical procedures which, with consummate skill, he has perfected and practiced during the first half of the present century and which have become standard techniques. I have selected myomectomy for discussion in Doctor Berg's honor as a tribute to of the masters from whom I had the privilege of learning the principles of surgical technique and many of the intellectual intangibles which the teacher inevitably imparts to his pupils.*

*This tribute was written while Doctor A. A. Berg was yet alive. It is keenly regrettable that he did not live to receive the plaudits of his friends, many colleagues, and patients. Probably none in his time served as many patients and few indeed there are who served so well.*

Myomectomy has gained increasing popularity among many gynecologists and a few general surgeons in the past thirty years, although hysterectomy is still preferred, perhaps, by the majority. The reasons why many have preferred hysterectomy date from experiences in the past era, when fear of sepsis, of blood loss without the availability of prompt transfusion, of shock, and other complications such as "ether pneumonia" made surgeons hesitant in performing myomectomies. It is not necessary to dwell upon the progress made during this interval in combating shock, in replacement of blood and in the availability of antibiotics and hemotherapeutic agents which have practically eliminated the danger of sepsis. Thanks to the newer chemotherapy and the advances in anesthesia, the danger of postoperative pneumonia has been appreciably minimized. Moreover surgical procedures, laboriously developed by the pioneers, have become so standardized as to enable the modern surgeon to perform operations with a degree of safety not dreamed of in the early part of this century.

Myomectomy serves two purposes. The more important one is that of conserving the power of reproduction. The second purpose is to conserve menstruation. In the majority of cases myomectomy is undertaken for the first but it also always accomplishes the second purpose. Fibroids of the uterus interfere with conception and pregnancy in several ways: 1) by blocking the access of the spermatozoa to the uterine cavity through distortion of the cervico-vaginal canal; 2) by blocking the approach of spermatozoa to the tubes through distortion, angulation, and physical blockage of the tubal ostia; and 3) by the frequently associated peritubal and periovarian adhesions. Chronic adnexitis has been variously reported. It occurred in about 9 per cent of Kelly and Cullen's series of 934 cases, in 27 per cent of McDonald's series of 700 cases and in 18 per cent of Frank's series of 400 cases. Moreover, periovarian adhesions occurred in 50 per cent of Kelly and Cullen's cases. Of 45 cases of fibroids examined by

uterotubal insufflation, only 15 showed normal tubal patency (1). The submucous variety of fibroid, as is well known, causes not only infertility because it acts as an obstruction, but also because it often prevents the normal progress of pregnancy.

These factors must be borne in mind in contemplating myomectomy in any given case. What determines in large part the indication for the operation is the attitude of the surgeon and his interest not only in conservative surgery but more especially in helping these women who still look forward to the possibility of motherhood.

Once the indication has been made for myomectomy there are two diagnostic measures which should be employed routinely. One is the determination of patency of the fallopian tubes and the degree of their function by uterotubal insufflation. The other is hystero-graphy in order to determine the configuration of the cavity of the uterus. These examinations are also essential in single women contemplating marriage. Knowledge of the presence of submucous fibroids or polyps associated with multiple fibroids is obviously very helpful in planning the operation because unless the submucous fibroid is large and easily recognized, it may be overlooked without a hystero-gram and remain behind after the other fibroids are enucleated. The same holds true of polypi, the presence of which must be determined beforehand, in order to remove them by a preliminary curettage. If a submucous fibroid is present, it can be removed either by the vaginal route as a preliminary step or, by the abdominal route in the course of myomectomy. In other words, it is well to orient oneself in the distribution, the location and the number of fibroids before the operation is begun. Awareness of the presence of non-patent tubes can aid both in formulating prognosis and in deciding upon the advisability of an operation.

In the course of the last 30 years several technical steps have been developed which have made the operation more safe. (1) To use as few uterine incisions as possible. Frequently, several fibroids can be removed through one incision. (2) The incision should be placed in the anterior wall of the uterus and fundus whenever possible. If incision on the posterior uterine wall becomes necessary, the wound should be covered by the sigmoid serosa or sigmoid epiploica. (3) The incision should be placed as far away from the uterine ends of the tubes as possible. (4) In sewing up the cavity of the tumor, the relation to the tube should be constantly kept in mind so that the lumen should not be closed by a suture.

The tumors are best removed by cutting deeply into their substance and grasping each bisected half with a tenaculum thus facilitating intracapsular enucleation (fig. 1). If one or more tumors extend into the uterine cavity, they may be enucleated without necessarily entering the cavity, the mucous membrane being gently peeled off from the myoma capsule. The exception is a submucous fibroid which has broken through its mucous covering and remains denuded for a smaller or larger area, in which case entry into the uterine cavity is unavoidable. The endometrium in such a case is sutured. Where a preliminary curettage has been done the uterine cavity will have been packed with iodoform gauze, which is readily identified and acts as a guide in sewing up the endometrial wound.

The fibroids are removed as far as possible through the same incision, extending it as the occasion requires in straight or curved fashion. Small subserous fibroids can be grasped with a single tenaculum hook and twisted out causing negligible bleeding. A fine catgut suture unites the serosa. Where deeper lying

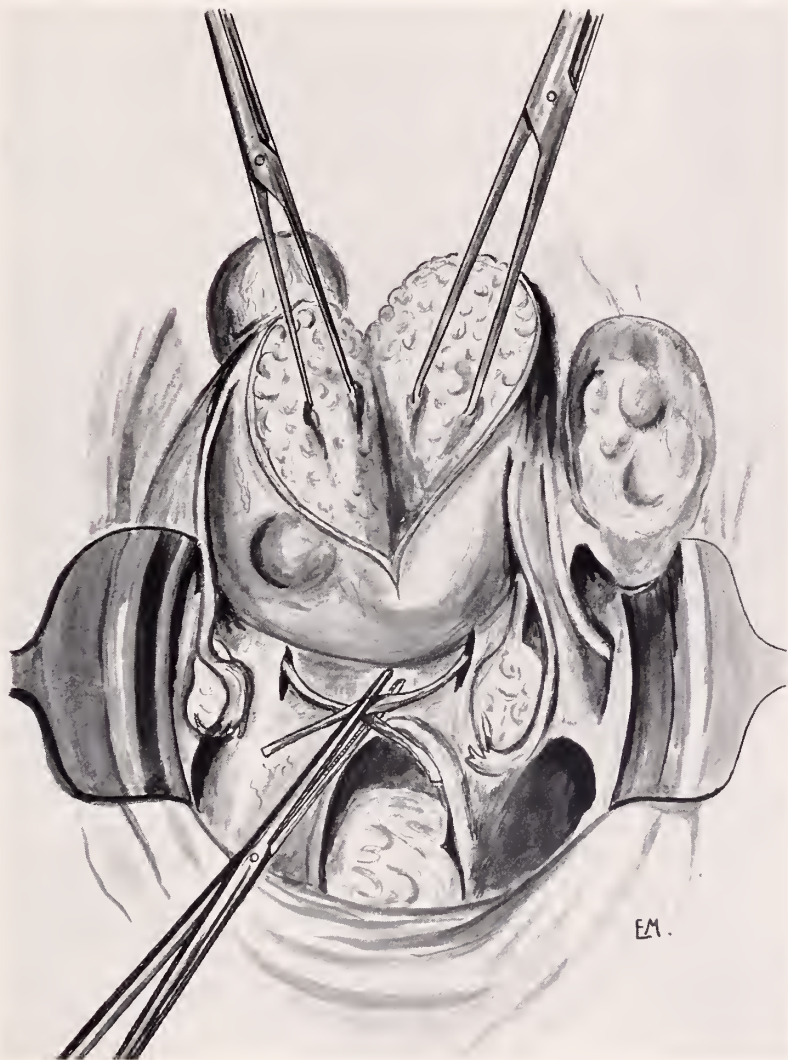


FIG. 1

tumors are removed a continuous or interrupted suture serves to obliterate the enucleated cavity. A seromuscular suture overlies this basic suture and a sero-serosal suture completes the wound closure of the uterus. No seromuscular segments are removed. It is better to leave *in situ* what appears as redundant and flabby seromuscular portions of the uterine wall, than to cut away segments in order to give the uterus a more symmetrical and compact appearance. The



uterine surface resumes its normal contour in about three months. Too much of the uterine wall should not be removed because it may put tension on the sutures with resulting necrosis, and more important because the uterine wall may become weakened in case pregnancy occurs.

The whole wound area is covered by one of two methods; either a flap of vesicouterine peritoneum is used to cover the whole wound area whenever this is possible, particularly when intraligamentous fibroids have been removed and/or a suture is taken from the anterior parietal peritoneum across and behind the topmost end of the uterine wound to the parietal peritoneum on the other side thus fixing it in ventrosuspension. Several fine sutures may be taken to support the uterus if it is heavy. The purpose of this procedure is to segregate the entire wound area from contact with the small intestines and to prevent intestinal obstruction. In former years intestinal obstruction was not uncommon due to adhesions between the small intestines, especially to necrotic hemorrhagic areas of the uterine surface. This should not occur more often than in the lower cervical Caesarean section where no sacrifice is made of the uterine wall and the entire wound is covered with vesicouterine peritoneum.

In case pregnancy takes place after myomectomy the adhesions resulting from the fine peritoneal serosal sutures stretch readily and cause no difficulty in the progress of gestation or with the process of labor. Caesarean section after multiple myomectomy is not an inevitable conclusion. A trial of normal labor is advised because in the vast majority of cases spontaneous delivery occurs.

A point that sometimes must be considered in the course of removing multiple fibroids is that one or two of the tumors appear suspicious of sarcoma. In such a case it is well to have a frozen section before closing the abdomen. Depending upon the pathological findings and other circumstances, chiefly nulliparity, and the keen desire of the patient and her husband for children, the surgeon is faced with the decision to proceed with a hysterectomy or not. In several cases where this dilemma arose, the writer has conserved the uterus and pregnancy followed once or several times. After many years of observation no secondary sarcoma has developed in these cases.

A similar problem presents itself when adenomyomata are encountered. In such cases although there is no question of malignancy the surgeon must decide between myomectomy and hysterectomy. In my experience it is better to remove these adenomatous tumors like in myomectomy and if it later becomes necessary, to resort to x-ray or radium therapy.

#### HEMOSTASIS

Perhaps the greatest progress made in myomectomy is in preventive hemostasis. The type of hemostasis is adapted to the variety of tumors and their distribution. A few isolated fibroids, especially the pedunculated and subserous variety, pose no special problem in securing hemostasis during their removal. The pedunculated fibroid is clamped at its pedicle and excised, the suture being passed around the clamp till the whole wound is closed. A broad thick pedicle may require clamping at each side. The incision is made at a point above the

clamps to allow for adequate imbrication of the seromuscular layers while each clamp is replaced by a suture ligature. An isolated large subperitoneal fibromyoma or one that is mostly intramural is incised down through its substance, each cut half being grasped with a tenaculum while the tumor is peeled out of its capsule by a hand sponge or the blunt end of the scalpel and then twisted so that a sort of pedicle is formed which can be clamped and ligated.

Should there be much bleeding as in a rich vascular myoma, the assistant can compress the broad ligaments between the fingers until the removal is completed, or, an intestinal or thyroid type clamp covered with rubber tubing can be applied snugly to each broad ligament to control the bleeding. Where a number of fibroids have to be removed, the use of such clamps is very useful. The choice of clamp will depend upon the area occupied by the fibroids and their distribution.

An intraligamentary fibroid is dealt with after the overlying fibroids have been removed. The vesico-uterine peritoneum is incised, preferably anteriorly, and with blunt dissection the flap is separated as widely as possible from the underlying tumor. The latter is then grasped by two tenaculæ on either side of its middle portion where the incision is made deeply so that the tumor can be removed subcapsularly. The special danger in removing intraligamentary fibroids is injury to the ureters; this can be avoided by enucleating the tumor and leaving the capsule *in situ*. Repair of the wound bed is the same as after removal of any other fibroid except that care should be taken not to include the ureters which should be identified whenever possible. If the intraligamentary fibroid is very large it is well to pass catheters into the ureters before the laparotomy. A pre-operative intravenous pyelogram is useful to determine whether or not the ureters are compromised.

When fibroids of all varieties are present and particularly when they are multiple and deeply intramural, placing an elastic ligature around the cervix just outside of the uterine vessels and compressing them by the taut tourniquet affords ideal preventive hemostasis. The ends of the tourniquet are passed through an avascular area of the broad ligaments by means of galley needles from one side around to the other. Kelly clamps may also be used to puncture the broad ligament and to grasp the end of the tourniquet on each side of the cervix. The elastic ligature is then pulled taut, crossed over and against the posterior cervix wall or lowermost portion of the lower uterine segment where it is secured at the point of crossing by a toothless clamp in order to avoid cutting the rubber tourniquet (fig. 1). This enables the surgeon to enucleate several tumors in a few minutes and practically bloodlessly. If many more than 5 or 6 tumors are to be removed, application of the ligature should not exceed 10 minutes when it should be relaxed; compression with hot pads will control the bleeding temporarily; after a minute the ligature can be made taut again and the remainder of the fibroids can be removed in the same manner. This point was learned from experience in an early case in 1941 in which shock followed the removal of 33 tumors without a pause (2). It has not been encountered since then in 87 myomectomies in which the elastic tourniquet was used 42 times. The perforations

in the broad ligament are closed by fine catgut sutures, two posteriorly and two anteriorly.

A solitary large subperitoneal and partly intramural fibroid springing from a broad area of the fundus of the uterus can be removed bloodlessly by placing 4 tenaculum forceps at four quarters of the circumference at the base of the tumor. The rubber tourniquet is passed through the tenaculae, held taut, crossed and clamped in the same way as above described. The removal of the fibroid proceeds as in the other variety and bleeding vessels are ligated separately if necessary. A hot pad is useful for this purpose which controls oozing temporarily, and is made secure by continuous suturing of the fibroid bed.

By using the broad ligament tourniquet the writer has been able to remove 88 fibroids from one uterus without inducing more shock than is expected after an ordinary hysterectomy. The postoperative convalescence compares favorably with that of hysterectomy while the mortality is less.

#### SUMMARY

The technique of myomectomy has for its primary object the safe removal of fibroids leaving the uterus intact. Steps in the procedure which have been found useful are (1) the making of the incision on the anterior aspect of the uterus whenever possible. (2) By removing as many tumors as possible through one incision. (3) By covering over the uterine wounds with vesicouterine peritoneum and (4) by segregating the entire wound area from the intestines by ventrofixation at a point behind and beyond the uterine wound.

To methods of preventive hemostasis already practiced has been added the method of temporary tourniquet constriction of the uterine vessels. By this method, many fibroids can be removed safely and practically without blood loss. The newer chemotherapy and antibiotics have added to the safety of the operation.

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## PROLAPSE OF THE UTERUS\*

### A REVIEW OF 722 CASES TREATED BY THE PARAMETRIAL FIXATION OPERATION

MORRIS A. GOLDBERGER, M.D., AND DAVID ZAKIN, M.D.

Various operations have been used during the past two decades for the correction of uterine prolapse. The general feeling has been that no one method is applicable in all cases. It is also generally recognized that the optimal approach is one that is entirely vaginal rather than abdominal and vaginal combined. It is our belief that the parametrial fixation or the Manchester operation is applicable in the large majority of cases, the main contraindication being the co-existence of uterine disease.

Danforth (1), in 1945, stressed that the operative management of uterine prolapse has been reduced to two methods almost to the exclusion of all others, i.e.: 1) vaginal hysterectomy, together with the use of the pelvic connective tissue condensations for support of the vaginal vault and bladder; and 2) the Manchester operation, utilizing the bases of the broad ligaments as the means of support, the cervix being shortened by amputation, and bladder advancement constituting an essential part of the operation. Phaneuf (2), on the other hand, lists seventeen procedures in the treatment of 900 patients with uterine and vaginal prolapse. The most frequent of these were the interposition operation (247 cases), vaginal hysterectomy (225 cases, including 41 by the clamp method), uterine suspension and vaginal plastic repair (133 cases) and the Manchester operation (106 cases). It will be noted that the Manchester operation was used by Phaneuf in approximately one out of ten cases of prolapse requiring operation (2-4). This operation was employed by the Michael Reese Hospital group (5) in 25.8% of 197 cases, by Collins *et al.* (6), in 35.1% of 128 cases, and by Gordon (7, 8) in 88.2% of 406 cases. At The Mount Sinai Hospital, New York City, the incidence of parametrial fixation in the operative treatment of uterine prolapse is approximately 95%. We agree with Berkeley and Bonney that vaginal hysterectomy is not justified in the treatment of uterine prolapse. Prolapse of the uterus results from damage of the supporting structures. Removal of the uterus may be followed by descent of the vagina, bladder and rectum, which may be avoided by repair of the damaged supporting tissues. However, if the uterus is left, the repair is made easier and the possibility of recurrence of prolapse is diminished.

In a number of institutions, including The Mount Sinai Hospital, parametrial fixation is recommended for all degrees of prolapse, including complete procidentia (5-8, 10-13); while, in others, complete procidentia is treated by vaginal hysterectomy, the parametrial fixation or other operations being reserved for lesser degrees of prolapse (1, 14-16). Some authors believe that the parametrial

\* From the Gynecological Service of the Mount Sinai Hospital.



fixation operation is particularly indicated in younger women where the possibility of future childbearing exists (14, 17-21), while others prefer uterine suspension combined with vaginal plastic repair as a sort of *pis aller*, realizing that eventual recurrence following delivery is probable (2, 22, 23).

It is not our intention here to enter into a discussion of the relative merits and demerits of these various operations, but rather to report our experience with one of them, the parametrial fixation operation. Every gynecologic surgeon has his preference, depending largely on his training, his ability to master a particular procedure to his satisfaction, and his subsequent experience with it; so that, if two or more operations are applicable to a given case, the natural tendency will be to choose the accustomed one. This holds true, in general, until the time sufficient evidence is presented of the preponderant advantages of a different procedure.

#### HISTORICAL

During the latter part of the nineteenth century, when Donald was Senior Resident at St. Mary's Hospital in Manchester, England, three different surgical procedures were employed in the treatment of uterine prolapse: cervical amputation, posterior colporrhaphy and perineorrhaphy, and narrowing of the vagina by anterior wall denudation. Results were almost uniformly poor; and operation was often resorted to with the rather negative idea of producing sufficient vaginal stenosis so that a pessary might be adequately retained to support the uterus. In 1888, Donald combined these procedures and, subsequently, as he developed his technique, incorporated the suturing of the cardinal ligaments. Within a short time, it became apparent that the operation *per se* effected a cure, and that the attendant use of a pessary was indeed unnecessary. The procedure, which became known as the Donald operation or the Manchester operation, enjoyed increasing popularity in England, and was later described in detail by Donald (24, 25). Operations based on the same anatomic principles but varying in technical approach were employed by Alexandroff (26), Tweedy (27), and Halban (as described by Mestitz) (28). Fothergill, a pupil of Donald, introduced a modification that permitted wider exposure and easier access to the bases of the broad ligaments, and more adequate fixation of the cardinal ligaments to the anterior aspect of the cervix. Fothergill's extensive writings served further to spread knowledge of this operation which began to be called also the Fothergill operation (29-32). Recently, Brentnall (33) has expressed his conviction that it was Fothergill rather than Donald who was responsible for the innovation of the parametrial stitch.

In this country, Maier and Thudium (10) reported in 1932 excellent results after lengthy experience with this operation. They also stressed the desirability of completing the procedure by repairing a coexisting defective perineum. In the same year, Frank (34), dissatisfied with the operative techniques employed at the time, particularly ventrofixation, introduced his modification of the Manchester operation for the treatment of uterine prolapse. In this preliminary report, dealing with a comparison of the various procedures, Frank found the

Manchester operation very promising, "because it fulfills the anatomical essentials, namely the bringing together of the bases of the broad ligaments as well as shortening of the pubocervical structures". Shaw (11), another pupil of Donald, read a paper in this country in 1933, describing his technique (which differed in some details from that of Donald and of Fothergill) and his excellent results. In 1935, Frank (12) published the details of his modification, which he termed the parametrial fixation operation. Gordon (7), in the same year, expressed his complete satisfaction with the operation, which, he felt, "accomplishes the most with the least risk". A number of other operators, both in England and in this country, have described their modifications, differing mainly in minor technical details from the original Manchester operation (5, 9, 15, 23, 35-38). Some of these are described in the excellent review of Frost (39).

Since Frank first began using the parametrial fixation operation 18 years ago, it has been the preferred operation at The Mount Sinai Hospital for the correction of uterine prolapse of all degrees. Except for minor changes, the procedure has remained essentially the same. Results obtained with the parametrial fixation operation at this hospital have been highly satisfactory and have warranted its continued use. Frank's (12) report in 1935 described excellent results in 106 ward and private patients. The next report on this operation emanating from The Mount Sinai Hospital was that of Salmon (40) in 1937. Salmon's series comprised 254 ward patients, and included additional follow-up on the ward patients of Frank's previous report. The present review is concerned with 722 consecutive ward patients with uterine prolapse who underwent the parametrial fixation operation at The Mount Sinai Hospital (in the services of Frank, Rubin, Geist, and Goldberger) during a fourteen-year period from 1933 through 1946. Included are some of Frank's and all of Salmon's cases for purposes of additional statistical analysis as well as lengthier follow-up study.

#### ETIOLOGY

Since prolapse most frequently results from stresses exerted over a fairly protracted period of time, a considerable proportion of cases are usually encountered in middle age and during senescence. In Collins' (6) series of 45 cases, the average age was 50. Shaw (11) reported that 171 of his 549 patients (31%) were over the age of 50. In our series of 722 patients, 233 or 32% had passed the age of 50; and 530 or 73% had passed the age of 40. The oldest was 79 years of age (table 1).

It is axiomatic that prolapse is most commonly due to anatomic and functional deficiency of the structures of the pelvic floor, resulting from parturition, spontaneous or instrumental. In Leventhal and Boshes' (5) series of 41 cases, 38 were parous; the average parity was 3. In our series, 708 patients or 98% were parous, the parity ranging from one to fifteen. Of our 708 parous patients, 610 (or six-sevenths) had had two or more children. The average parity was 3.1 (table 2).

Finally, a precipitating factor may often be the atrophy and diminished tonus of pelvic structures appearing after the climacteric. Thus, a previously "latent"

or potential prolapse may become actual after the menopause; or a prolapse of 1st or 2nd degree may become complete under the influence of post-menopausal atrophy. In our series, 334 patients or 46% were post-menopausal. Of these, 159, or almost one-half, had experienced the menopause five to thirty-five years before (table 3).

TABLE 1

AGE	NUMBER
20-25 years	3
26-30 years	16
31-35 years	55
36-40 years	118
41-45 years	141
46-50 years	156
51-55 years	104
56-60 years	80
61-65 years	30
66-70 years	11
71-75 years	7
76-80 years	1
Total.....	722

TABLE 2

PARITY	NUMBER
0	14
1	98
2	216
3	171
4	88
5	60
6	38
7	15
8	6
9	5
10	5
11	3
12	1
13	1
15	1
Total.....	722

In nulliparous women, developmental defects of the supporting pelvic structures have been incriminated. In our series, 14 women or 1.9% were nulliparae. The incidence of nulliparity in Maier and Thudium's (10) group was 4.4%, and in that of Leventhal and Boshes (5), 7.3%. In Shaw's (11) series, there were 32 nullipara out of 549 patients, or 5.8%. The latter notes that prolapse in the

multiparous woman, while extremely rare in the South of England, is not infrequent in the industrial North, since many of these women undertake heavy work, which serves to increase intra-abdominal pressure and further weaken congenitally defective structures.

In rare cases, occult spina bifida, with its accompanying nerve disturbances, may be responsible for sphincter weakness, bladder dysfunction and uterine prolapse in nulliparae (41). We have not encountered such cases in our group.

#### DEGREE OF PROLAPSE

The various terms used to designate descent of the uterus from its normal position include prolapse (or prolapsus uteri), descensus and procidentia. It is customary to differentiate between various degrees of prolapse. Here, uniformity is conspicuous by its absence—two, three and even four degrees of prolapse being recognized by various authors, with corresponding variations in landmarks (4, 5, 7, 42-46).

TABLE 3

YEARS POST-MENOPAUSAL	NUMBER
Less than 1 year	39
1- 5 years	136
6-10 years	71
11-15 years	46
16-20 years	22
21-25 years	13
26-30 years	5
31-35 years	2
Total.....	334

It is problematical whether classification of prolapse into as many as four degrees is necessary or desirable. In fact, it would seem that, for all practical purposes, classification into two degrees, such as incomplete and complete, might be adequate. However, mainly for purposes of comparison, it has been our custom to consider three degrees of prolapse, as follows: 1st degree prolapse is descent of the cervix to the introitus; 2nd degree prolapse is protrusion of the cervix at least one and one-half inches beyond the introitus; and 3rd degree prolapse is complete protrusion of the uterus, with the fundus palpable at or below the introitus.

In Collin's (6) series of 45 cases, there was 1st degree prolapse in 69%, 2nd degree prolapse in 15.5%, and 3rd degree prolapse in 15.5%. Gordon's (7) first group of 170 cases consisted of 1st degree prolapse in 45.3%, 2nd degree prolapse in 33.5%, and 3rd degree prolapse in 21.2%. In his later report (8), dealing with 206 cases, 1st degree prolapse constituted 56.8%, and 2nd and 3rd degree prolapse grouped together constituted 43.2%. In our series, the division



is as follows: 1st degree prolapse, 63.7%; 2nd degree prolapse, 23.5%; and 3rd degree prolapse, 12.8% (table 4).

#### DURATION OF PROLAPSE

How much time elapses between the discovery of prolapse and its operative correction depends on a number of factors. Many women, because of timidity or fear, tolerate the inconveniences of prolapse for many years before submitting to operation. Some manage to carry on with the use of pessaries until they are no longer retained; and others are obliged to discontinue them because of traumatic ulceration and infection of the vagina. A number of our patients had had

TABLE 4

DEGREE OF PROLAPSE	NUMBER	PERCENTAGE
1st degree	460	63.7%
2nd degree	170	23.5%
3rd degree	92	12.8%
Total	722	

TABLE 5

DURATION OF PROLAPSE	NUMBER
Less than 1 year	135
1-5 years	338
6-10 years	96
11-15 years	46
16-20 years	37
21-25 years	17
26-30 years	7
31-35 years	1
Not determined	45
Total	722

prolapse for many years, during which time, one or more operations afforded relief for varying periods until recurrence took place. In our series, the shortest duration of prolapse was one week; and the longest was 34 years. Two-thirds of the patients underwent parametrial fixation operation within five years of the appearance of prolapse (table 5).

From the point of view of serious repercussions on the patient's health, protracted duration of prolapse of minor degree, though undesirable, is less important than that of complete prolapse. When prolapse of considerable extent continues without adequate support, dilatation of the ureters and kidneys may set in, followed by infection and renal damage. The possible anatomical factors involved are: 1) stretching and narrowing of the intramural portions of the ureters; 2) compression of the ureters by the pelvic floor through which the mass

prolapses; and, probably most important, 3) constriction of the ureters by the uterine arteries which are dragged down over them (42). This last factor has been emphasized by Brettauer and Rubin (47).

In advanced degrees of prolapse, particularly of long duration, intravenous urography, blood chemistry determinations, and renal function tests are advisable, in addition to urine examination. In most cases, operative cure of the prolapse is followed by considerable regression of the ectasis and improvement of kidney function. The most extreme degree of hydroureter and hydronephrosis, accompanied by marked diminution in kidney function, was observed in a case of 3rd degree prolapse of two years duration, with irreducibility for one year (*v.i.*).

#### ASSOCIATED CONDITIONS

Cystocele, rectocele or, more usually, combinations of both, are frequent concomitants of uterine prolapse. In order to compare more adequately the post-operative results with the preoperative status, both cystocele and rectocele are graded according to size, as small, moderate and large.

In Leventhal and Boshes' (5) series of 51 patients, parametrial fixation was done for prolapse in 41, for elongation, hypertrophy and laceration of the cervix in 4, and for cystocele in 6. Of the 41 cases of prolapse, there was associated cystocele in all 41, and rectocele in 36. In Collins' (6) group of 45 cases of prolapse, cystocele was present in 42, and rectocele only in 5. Gordon (7) noted that cystocele and rectocele occurred in 142 of 170 patients with prolapse. In our series of 722 patients with prolapse, cystocele was present in 656 and rectocele in 670 (table 6). In the large majority of cases, the two conditions were coexistent. There was a definite tendency for cystocele to attain a larger size than rectocele. In only 11 cases, was there neither cystocele nor rectocele. In practically all cases, the perineum was relaxed or lacerated.

Urinary incontinence, mainly of the stress variety, was present in 172 patients, an incidence of 24%, in contrast to Shaw's (11) incidence of 3%. Incontinence need not necessarily be associated with urethrocele, which was noted in only 27 of our patients. Enterocele was relatively uncommon, occurring in only 9 cases. Recognition of coexisting enterocele and its repair are of utmost importance, since many cases of supposedly recurrent rectocele are actually occult enteroceles.

A number of other gynecological conditions, including 32 cases of fibroid uterus and 29 cases of functional uterine bleeding, were encountered in our series. These are indicated in Table 6.

#### STATE OF THE CERVIX

Hypertrophic, infectious and ulcerative changes in the prolapsed cervix are extremely common. Even when the cervix appears unaffected on inspection, microscopic examination frequently reveals the presence of disease. When part or all of the uterus protrudes from the introitus, ulceration of the cervix and/or

vagina is almost the rule. This is due partly to irritation from rubbing against neighboring skin areas, vulvar pads or clothing, and partly to circulatory interference, with congestion and edema. The accompanying vaginal discharge frequently irritates the vulva and the skin of the perineum and thighs.

Of our 722 patients, an adequate clinical description of the cervix was noted in 580. Of these, the cervix was clean, atrophic or both in 91 cases, and grossly diseased in 489 (table 7). The diagnoses included various degrees and combinations of hypertrophy, elongation, eversion, edema, ulceration, erosion, cornifica-

TABLE 6

ASSOCIATED CONDITIONS	NUMBER	
Cystocele.....		656
small.....	72	
medium.....	225	
large.....	359	
Rectocele.....		670
small.....	234	
medium.....	292	
large.....	144	
Incontinence, mainly stress.....		172
Urethrocele.....		27
Enterocoele.....		9
Fibroid uterus.....		32
Menometrorrhagia.....		29
Adenomyosis.....		1
Ovarian cyst.....		2
Ovarian tumor.....		1
Bleeding from cervical stump.....		2
Perineo-vaginal fistula.....		1
Perineal cyst.....		1
Ulceration of vagina due to pessary.....		2
Synechiae of vagina (post-radiation).....		1
Diabetic vulvitis.....		1
Urethral caruncle.....		1
Urinary retention.....		1
Rectal polyp.....		1
Rectal prolapse.....		1
Hemorrhoids.....		5

tion and nabothian cyst formation. The pathologic diagnosis of the amputated cervixes was available in 584 cases. Of these, only two could be considered normal. In 582 of 584 cases, or 99.6%, the cervix was histologically diseased (table 7). In the large majority of cases, the pathologic diagnosis was chronic endocervicitis, with or without nabothian cyst formation. Other frequent diagnoses were acute endocervicitis, acute and chronic erosion, acute and chronic ulceration, and polyp. Less common diagnoses were: papillary endocervicitis (13 cases), leukoplakia (5 cases), hornification of squamous epithelium (3 cases), chronic endocervicitis with marked epithelial proliferation (1 case), and subacute ne-

crotizing arteritis of the cervix (1 case). Intensive investigation of the latter patient failed to reveal evidence of periarteritis nodosa or other diffuse vascular disease. There were also 4 cases of unsuspected early cervical carcinoma (*v.i.*).

The relative rarity of cervical malignancy in prolapse has caused considerable conjecture, in view of the extreme prevalence of inflammatory lesions, including ulceration and erosion. It has been suggested that the immunity to malignant change is due to good drainage, preventing retention of chemically changed, irritating secretions (44).

In Shaw's (11) series of 549 cases, there is no mention of cervical malignancy having been encountered. Leventhal and Boshes (5) found no malignancy in their series of 51 cases; and, similarly, Collins (6) found none in 45 cases. In Gordon's (7) series of 170 cases, 1 case of unsuspected cervical carcinoma was discovered by pathologic examination, an incidence of 0.6%. In our series, a number of cervixes were biopsied preoperatively because of extensive erosion or

TABLE 7

STATE OF THE CERVIX		NUMBER	
Clinically			
Not described			142
Described			580
Not diseased	91		
Diseased	489		
Microscopically			
Not described			138
Described			584
Not diseased	2		
Diseased	582		

ulceration; all proved benign. However, in 4 cases, which appeared entirely benign clinically, routine pathologic examination of the extirpated cervixes revealed early carcinoma. (Two of these cases have been previously reported by Rubin (48).) The incidence is 4 out of 584, or 0.7%.

#### PREVIOUS OPERATIONS

A number of our patients had had one or more previous operations by the vaginal or combined vaginal and abdominal routes, done at other institutions for prolapse of the uterus and associated states. The various procedures included: anterior and posterior colporrhaphy (32 cases), ventrofixation combined with anterior and posterior colporrhaphy (10 cases), uterine suspension combined with anterior and posterior colporrhaphy (5 cases), interposition operation (6 cases), hysteropexy and Polk repair (1 case), and unspecified vaginal plastic operations (7 cases) (table 8). These patients with recurrent prolapse represented a challenge to the parametrial fixation operation, a challenge which was successfully met, as will be shown below.

Some had also undergone various operations on the uterus and adnexa, in-



cluding 41 cases of supravaginal hysterectomy (followed by prolapse of the cervical stump) and 1 case of total hysterectomy (followed by prolapse of the vaginal vault). There were also a number of miscellaneous gynecologic procedures, mainly of a plastic nature, as well as non-gynecologic abdominal operations (appendectomy, cholecystectomy, herniorrhaphy) (table 8).

TABLE 8

PREVIOUS OPERATIONS	NUMBER	
Operations for prolapse, etc. ....		61
Anterior and posterior colporrhaphy .....	32	
Ventrofixation combined with anterior and posterior colporrhaphy .....	10	
Uterine suspension combined with anterior and posterior colporrhaphy .....	5	
Interposition operation .....	6	
Hysteropexy and Polk repair .....	1	
Unspecified vaginal plastic operations .....	7	
Gynecologic abdominal operations .....		92
Supravaginal hysterectomy .....	41	
Total hysterectomy .....	1	
Salpingo-oophorectomy and salpingectomy .....	17	
Oophorectomy .....	10	
Myomectomy .....	8	
Tubal ligation .....	8	
Cesarian section .....	7	
Miscellaneous plastic operations .....		17
Urethroplasty .....	5	
Reverse plastic .....	2	
Repair of perineal laceration .....	4	
Trachelorrhaphy .....	4	
Cervical polypectomy .....	2	
Non-gynecologic abdominal operations .....		102
Appendectomy .....	37	
Cholecystectomy .....	36	
Herniorrhaphy (inguinal, femoral, umbilical, incisional) ...	29	

## PREOPERATIVE MANAGEMENT

An integral part of the preoperative care of any surgical patient is complete evaluation of the medical status by thorough general physical examination, supplemented by indicated laboratory, radiologic or other examinations. This is particularly necessary in the older age groups where the incidence of degenerative disease is high. When any complicating condition is found, consultation is made with the proper department (medicine, surgery, anesthesiology, etc.) and the recommended therapy, if any, is instituted. The most common medical conditions discovered in our series were essential hypertension (61 cases), hyperten-

sive cardiovascular disease (17 cases), and diabetes (17 cases). There were a number of other conditions of lesser frequency, as shown in Table 9. In the large majority of cases, there were no contraindications to operation, which was performed with little or no delay.

However, in a small number of patients, it was necessary to defer operation for several weeks or months, mainly because of local conditions requiring preliminary treatment. Thus, there were 2 cases of severe genito-crural epidermophytosis, 1 case of acute dermatitis and pruritus of the vulva and perianal region due to urinary incontinence, 3 cases of marked cervicitis with profuse purulent

TABLE 9

COMPLICATING CONDITIONS	NUMBER
Essential hypertension	61
Hypertensive cardio-vascular disease	17
Rheumatic heart disease, compensated	3
Anginal syndrome	3
Chronic nephritis	1
Renal calculus	1
Bilateral hydronephrosis and hydroureter	4
Pulmonary tuberculosis, arrested	3
Emphysema, marked	3
Chronic cholecystitis and cholelithiasis	8
Peptic ulcer	1
Chronic ulcerative colitis	2
Diabetes	17
Obesity	6
Hyperthyroidism	4
Non-toxic thyroid adenoma	5
Lues	4
Pernicious anemia	2
Secondary anemia, severe	1
Psychoneurosis	5
Hernia (incisional, inguinal, femoral, umbilical)	6
Varicose veins, severe	2

leucorrhea, 2 cases of acute trichomonas vaginalis vaginitis, 2 cases of ulceration of the vagina due to prolonged indwelling pessary, 1 case of labial furuncle, 1 case of infected Skene's glands, 3 cases of severe ulceration of the cervix in 3rd prolapse, and 1 case of diabetic vulvitis. In 3 patients, preliminary biopsy of the cervix was done because of suspicious erosion; in all 3, no malignancy was found. In 2 cases, the uterus was curetted, as a separate procedure, because of profuse menometrorrhagia; malignancy was not found. In 1 patient, D. and C. (which is done routinely just prior to the operation itself) produced a large amount of curettings, which appeared grossly like placental tissue. The operation was deferred until after the pathologic examination, which revealed hyperplastic endometrium with decidual reaction. In another patient, routine curettement showed the presence of an early unsuspected pregnancy; operation was performed 6

weeks later. In a few instances, operation was postponed because of general medical conditions, such as diabetes discovered on admission and previously unknown to the patient (2 cases), thyrotoxicosis with auricular fibrillation (1 case), marked obesity (3 cases), and upper respiratory infection (3 cases).

Infections of the urinary tract require preoperative treatment, preceded, when indicated, by cystoscopy and pyelography (intravenous or retrograde).

Small ulcerations of the cervix or vagina without gross infection do not contraindicate operation. Large, infected decubitus ulcers are treated preoperatively by reposition of the prolapsed uterus with the aid of pessaries or tampons treated with glycerite of boroglycerine or Lassar's paste. Penicillin vaginal suppositories have been found effective in reducing infection. On occasion, estrogens, systemically and locally, have been employed with success. Tub baths and bed rest are useful adjunct measures.

Each patient is typed and cross-matched, and 500 cc. of blood are held in reserve. Seconal is administered the evening prior to operation, and also in the morning if operation is scheduled for the afternoon. The patient receives a vaginal douche of 2 quarts of warm tap water the morning of operation. Preoperative medication at present usually consists of demerol 100 mg. and scopolamine gr. 1/150. An intravenous infusion of normal saline solution with 5% glucose is started 2 hours before operation.

#### OPERATIVE PROCEDURES

In our series of 722 patients, there were 680 with prolapse of the uterus, 41 with prolapse of the cervical stump, and 1 with prolapse of the vaginal vault. Parametrial fixation of the uterus was done in 661 cases, parametrial advancement<sup>1</sup> of the uterus in 19 cases, parametrial fixation of the cervical stump in 40 cases, parametrial advancement of the cervical stump in 1 case, and parametrial fixation of the vaginal vault in 1 case. In addition, 4 patients with recurrent prolapse after previous parametrial fixation were again subjected to the operation. Thus, a total of 726 parametrial procedures were performed (table 10).

Dilatation and curettage was done routinely in practically all cases. In no instance, did the curettings show malignancy. Only 11 patients did not require colporrhaphy; of these, 10 had had previous vaginal plastic operations. Anterior and posterior colporrhaphy and perineorrhaphy was done in 651, anterior colporrhaphy in 35, and posterior colporrhaphy and perineorrhaphy in 25. Urethroplasty of the Kelly type was performed in 73 patients and enterocele was repaired in 6. The tubes were ligated in 35 patients. In 5 cases, vaginal supravaginal hysterectomy, and in 4 cases, vaginal myomectomy preceded parametrial fixation. In 2 patients with irreducible prolapse (*v.i.*), laparotomy was done as a first stage procedure to reduce the prolapse, prior to parametrial fixation as the second stage. In addition, there were a number of concomitant miscellaneous procedures, as shown in Table 10.

<sup>1</sup> Parametrial resection and advancement is a modification proposed by Rubin, especially for 3rd degree prolapse. This operation will be the subject of a separate report by Rubin (49).

General inhalation anesthesia was employed in the large majority of cases. In 15 patients, operation was performed under local anesthesia.

POSTOPERATIVE MANAGEMENT

Indwelling catheter is not employed. The patient is catheterized every 6 to 8 hours until the residual urine measures 60 cc. or less on 2 occasions. Spontaneous micturition usually appears on the fourth or fifth day. Morphine gr.  $\frac{1}{6}$  is administered whenever necessary during the first 2 postoperative days. The vaginal

TABLE 10

OPERATIVE PROCEDURES	NUMBER
Parametrial fixation of uterus	665
Parametrial advancement of uterus	19
Parametrial fixation of cervical stump	40
Parametrial advancement of cervical stump	1
Parametrial fixation of vaginal vault	1
Anterior and posterior colporrhaphy and perineorrhaphy	651
Anterior colporrhaphy	35
Posterior colporrhaphy and perineorrhaphy	25
Urethroplasty	73
Enterocoele repair	6
Tubal ligation, vaginal	31
Tubal ligation, abdominal	3
Tubal ligation and salpingo-oophorectomy, vaginal	1
Supravaginal hysterectomy, vaginal	5
Myomectomy, vaginal	4
Hemorrhoidectomy	5
Repair of incisional hernia	1
Repair of rectal prolapse	1
Repair of old laceration of anal sphincter	1
Excision of rectal polyp	2
Excision of lipoma of buttock	2
Excision of naevus of buttock	1
Excision of perineo-vaginal fistula	1
Excision of perineal cyst	1
Excision of cyst of labium majus	1
Excision of bartholin cyst	1
Excision of urethral caruncle	1

packing is removed on the morning of the third day, and an enema is administered. The patient is usually ambulatory on the third day or sooner, if her condition permits. If appreciable vaginal secretion is present on the seventh or eighth day, vaginal douches are instituted. Discharge from the hospital, usually on the tenth to twelfth day, is preceded by a vaginal examination and a notation on the record of the pelvic status. The patient is then referred to the follow-up clinic in 2 or 3 months, and is re-examined there at intervals of 6 months, unless more frequent visits are indicated.



## MORBIDITY, COMPLICATIONS AND MORTALITY

In Leventhal and Boshes' (5) series, 15 of 51 patients (29%) were morbid, the causes being cystitis, pyelitis, parametritis, thrombophlebitis, perineal wound infection and secondary hemorrhage. These authors note that the "morbidity from the Manchester operation compares favorably with the morbidity following the two other operations most commonly used for prolapse and cystocele in our institution the past ten years", i.e., vaginal hysterectomy and the interposition operation. In Collins' (6) series of 45 cases, the postoperative course was smooth, except for 2 postoperative complications (1 secondary hemorrhage and 1 persistent pyuria), and a few cases of acute cystitis, readily responsive to sulfonamide therapy. Gordon's (7) series of 170 cases (for which parametrial fixation was done in 152) included the following postoperative complications: pelvic cellulitis and parametritis (8 cases), secondary hemorrhage (2 cases), thrombophlebitis (2 cases), pulmonary embolism with recovery (2 cases), psychosis (1 case), strangulated hemorrhoid (1 case), and cellulitis of the arm due to injection (1 case).

In our series of 722 cases, there were 35 cases of proved urinary tract infection (22 cystitis, 11 pyelitis, 2 infected hydronephrosis). In addition, there were 87 patients who had a temperature of 101°F. or over for two or more days. In all probability, the morbidity in most of these patients was due either to mild cystitis or low-grade infection at the operative site. The occurrence of cystitis following vaginal plastic surgery is related to preexisting urinary tract infection, operative trauma to the bladder, and catheterization. Much can be done to reduce the incidence of cystitis by adequate preoperative and postoperative chemotherapy, avoidance of undue trauma or excessive manipulation of the trigone and base of the bladder during operation, and minimal catheterization under aseptic precautions.

Thrombophlebitis occurred in 15 patients; of these, 4 had clinical or radiologic evidence of pulmonary infarction. Conservative therapy in 13 was followed by recovery in all cases. Femoral vein ligation was employed in 2 patients; 1 recovered and 1 died (*v.i.*). There were 5 cases of mild to moderate postoperative shock, requiring blood transfusion. Other less frequent postoperative complications are listed in Table 11.

Local complications are relatively uncommon. Of these, the most important is secondary hemorrhage, usually occurring about 1 week after operation, and probably due to low-grade infection preventing adequate wound healing. The most frequent site of bleeding is the cervix. Secondary hemorrhage occurred in 5 of our patients. In 3, the bleeding was from the cervix, and was controlled by packing; in 1, the bleeding was due to separation of the perineal wound, and was controlled by pressure; and in 1, bleeding from the entire vaginal suture line required secondary suture. Local infectious processes included 1 case of pelvic cellulitis, 1 case of purulent inflammation of the paracervical tissue, and 2 cases of suppurative of the perineal wound, followed by breakdown of the wound in 1 case (table 11).

Operative injury to urinary tract structures is quite rare, and, if promptly

recognized, repair should be followed by no untoward sequelae. In our series, there was 1 case of operative injury to the urethra which was immediately re-

TABLE 11

MORBIDITY, COMPLICATIONS AND MORTALITY	NUMBER	
Temperature 101° or over for 2 or more days . . . . .		87
Cystitis . . . . .		22
Pyelitis . . . . .		11
Infected hydronephrosia . . . . .		2
Thrombophlebitis (with pulmonary infarction in 4) . . . . .		15
Conservative therapy . . . . .	13*	
Femoral vein ligation . . . . .	2†	
Post-operative shock, mild to moderate . . . . .		5
Pneumonia . . . . .		5
Atelectasis . . . . .		2
Upper respiratory infection . . . . .		6
Anginal syndrome . . . . .		1
Exacerbation of chronic cholecystitis . . . . .		1
Diabetic ketosis, mild . . . . .		1
Cellulitis of arm and of thigh (following injection) . . . . .		2
Parotitis (with spontaneous subsidence) . . . . .		1
Brachial plexus palsy (with recovery) . . . . .		1
Herpes zoster . . . . .		1
Anxiety neurosis . . . . .		2
Psychosis, mild . . . . .		1
Local conditions . . . . .		9
Secondary hemorrhage from cervix . . . . .	3	
Secondary hemorrhage due to separation of perineal skin . . . . .	1	
Secondary hemorrhage from suture line (requiring repair) . . . . .	1	
Pelvic cellulitis . . . . .	1	
Purulent inflammation of paracervical tissue . . . . .	1	
Perineal suppuration . . . . .	2	
Urinary tract operative injury . . . . .		4
Urethral injury with immediate repair . . . . .	1	
Ureterovaginal fistulae with spontaneous healing . . . . .	2	
Bilateral ureteral ligation with subsequent release of sutures and recovery . . . . .	1	
Post-operative anatomic imperfections . . . . .		50
Vaginal shortening or constriction . . . . .	34	
Granulation tissue in vaginal vault . . . . .	8	
Denudation of cervix . . . . .	4	
Vaginal synechiae . . . . .	3	
Cervical stenosis with pyometra . . . . .	1	
Mortality . . . . .		2

\* Recovery in all cases.

† 1 recovery and 1 death.

paired, 2 cases of postoperative ureterovaginal fistula which healed spontaneously, and 1 case of accidental ligation of both ureters which was recognized and corrected within 24 hours after operation.

Follow-up examination during the weeks or months following discharge from the hospital may reveal various anatomic imperfections, such as vaginal shortening or narrowing, granulation tissue in the vaginal vault, denudation of the cervix, vaginal synechiae, or cervical stenosis with hematometra or pyometra.

In Shaw's (11) series of 549 cases, there were only 2 cases of narrowed vagina; both were treated by digital dilatation under anesthesia. Our experience was less fortunate, possibly because the majority of the cases are utilized for training of residents and younger members of the staff. There were 34 patients, in whom the vagina was shortened or constricted. In about one-half, this was unavoidable because of scar tissue due to previous vaginal plastic operations. In most cases, dyspareunia disappeared spontaneously or after gradual dilatation; in 2 cases, reverse plastic operation resulted in cure.

Granulation tissue in the vaginal vault was encountered in 8 patients, and responded readily to cauterization. Denudation of the cervix in 4 cases was followed by secondary healing. Vaginal synechiae were found in 3 cases. No treatment is necessary if the patient is not sexually active. However, if coitus is painful, digital stretching or incision under anesthesia is indicated.

Postoperative stenosis of the cervix is relatively rare. Callagher (50) recently reported 2 isolated cases of hematometra due to cervical stenosis occurring 3 years and 1 year respectively after parametrial fixation. As a prophylactic measure, he recommends passage of a small dilator at the time of the postoperative examination. Shaw (11) reports only 1 case in his series of 549 patients. Every month for 4 months after operation, this patient experienced severe lower abdominal pains and failed to menstruate. Passage of a sound into the cervix was followed by release of hematometra. In Gordon's (7) series of 152 cases of parametrial fixation, there were 3 cases of hematometra. He states that it had not been his practice at the time to thoroughly dilate the cervical canal as recommended by Fothergill and Shaw. Thorough cervical dilatation is a routine procedure at The Mount Sinai Hospital; it is probably for this reason that our incidence of cervical stenosis is extremely low—1 case in 722.

In the series of 549 patients reported by Shaw (11), there were no fatalities. However, he states that, during a 26 year period, he performed a total of 2,152 Manchester operations, with 9 deaths, a mortality rate of 0.41%. The causes of death were: pneumonia (1 case), heart failure (1 case), embolism (1 case), pyelitis (1 case), septic absorption from gauze retained in the uterus (1 case), and unknown (4 cases). There were 2 deaths in our series, an incidence of 0.27%. One was due to pulmonary embolism, and the other to accidental irrigation of the bladder with ammonia water, resulting in gangrenous cystitis, suppurative pyelonephritis and septicemia.

#### IRREDUCIBLE PROLAPSE

Despite its extreme rarity, irreducible prolapse of the uterus merits special mention in this review because of the surgical problems involved. Two cases have been encountered in this series; both have been reported at length by Frank (51, 52). Because of the special interest of this condition, short resumsés of these

cases will be presented here. Frank, who had surveyed the literature, could find few instances of irreducible prolapse. One case observed by v. Jaschke (53) recovered spontaneously after gangrene and sequestration of the major portion of the uterus. Beyea's (54) patient underwent vaginal hysterectomy; death from peritonitis occurred 5 days later. Baldy (55) was able to reduce the prolapse in his patient by manipulation; abdominal hysterectomy, fixation, and vaginal repair, performed 1 week later, were followed by recovery. By vaginal manipulation, preceded by knee-chest position for one and one-half hours, Slocum (56) reduced a case of prolapse, which had become irreducible a short time before.

#### ILLUSTRATIVE CASES

*Case 1.* M. O'C., a 42 year old para II, who had a complete prolapse of the uterus for 1 year, was admitted because of irreducibility since 2 weeks, and signs of intestinal obstruction since 2 days. The huge mass protruding from the vulva was cyanotic, edematous and ulcerated; tympanic percussion note and gurgling on pressure indicated the presence of bowel in addition to uterus, bladder and rectum. Attempts at manual reduction were unsuccessful, and signs of intestinal obstruction increased. Consequently, the next day on January 8, 1937, laparotomy was performed. Omentum was adherent anteriorly above the pubis and loops of small intestine were matted together by fibrin. To gain access to the pelvis and the hernial mass below it, the distended colon was decompressed by insertion of a needle. Exploration, which was now possible, revealed the presence of a sliding hernia of the cecum along with the appendix and terminal ileum, in addition to the uterus and bladder. Continuous pressure exerted from below by assistants resulted finally in reduction of the prolapse so that the herniated organs sprang into view. The abdominal wound was then closed, and the vagina was packed to prevent recurrence of the prolapse. The intestinal obstruction was relieved, and bowel function was satisfactorily established. The postoperative course was stormy, complicated by pneumonia and protracted wound infection. The patient remained in bed for almost 5 weeks and, on arising, prolapse recurred but was readily replaceable. Parametrial fixation, which was done on March 6, 1937, 2 months after the first operation, was followed by an uneventful convalescence. Follow-up examination 14 months later showed cure of the prolapse.

*Case 2.* L. K., a 56 year old para I, was referred to the Gynecology service on January 4, 1946 by Dr. R. T. Frank because of 3rd degree prolapse of 2 years duration, which had become irreducible since 1 year; large, firm, globular, movable, nontender suprapubic mass; bleeding from the cervix of long duration; and severe secondary anemia. The hemoglobin on admission was 11%. Marked bilateral hydronephrosis was demonstrated by intravenous pyelography; the blood urea was 9 mg. per cent, the maximal urinary concentration was 1.012, and the P.S.P. test showed greatly diminished kidney function (less than 10% excretion). The situation was further complicated by paranoid trends, an unusual degree of uncooperativeness, and a phobia for any form of injection therapy. Nevertheless, 4 blood transfusions of 500 cc. each were administered during the next 2 weeks. Laparotomy was performed on January 17, 1946. The suprapubic mass was identified as a solid ovarian tumor obstructing the pelvic inlet, with a thick pedicle descending into the herniation. Traction was made from above, while pressure was exerted from below by an assistant. With this combined maneuver, the prolapse was reduced, and the uterus and bladder appeared. Supravaginal hysterectomy and bilateral salpingo-oophorectomy were done. The pathologic report was granulosa-theca cell tumor of the ovary, adenomyosis and fibromyomata of the uterus, with hyperplasia of the endometrium. The vagina was packed to help maintain the reduction. The postoperative course was stormy and, for a time, even desperate. Bronchopneumonia, severe urinary tract infection with hematuria, and bacteremia finally responded to sulfadiazine, penicillin, blood transfusion, oxygen and adjuvant medication. Convalescence continued satisfactorily, and the patient went home on



February 7, 1946, the twenty-first postoperative day. A repeat P.S.P. test before discharge showed improved renal function (30% excretion). While at home, the prolapse recurred but could be readily replaced. There were several bouts of urinary tract infection.

One month later, when she was readmitted for repair of the prolapse, the hemoglobin was 60%, there were many white blood cells in the urine, urine culture showed *B. pyocyaneus*, and urinary concentration did not exceed 1.010. On March 21, 1948, parametrial fixation was performed; because of the extreme shortness of the cervical stump, this was excised, and the two parametria were united in the midline. Streptomycin was administered postoperatively; although fever disappeared, urine cultures remained consistently positive for *B. pyocyaneus*. Convalescence was otherwise uneventful, and the patient was discharged on April 15, 1946. P.S.P. test done before discharge showed continued improvement of renal function (55% excretion). Intravenous pyelography demonstrated some diminution of hydroureter and hydronephrosis. Follow-up examination on June 12, 1946 showed that the vaginal vault remained high. The patient is at present in good health, and has had no recurrence of urinary tract infection.

Results of primary vaginal operation for irreducible prolapse have been unsatisfactory. Congestion, edema and infection of the prolapsed mass render the vaginal approach extremely hazardous. Frank believes the primary operation should be abdominal to remove any existing cause of irreducibility and to facilitate reduction. Subsequently, the prolapse may be operated on vaginally in the customary manner. His recommendation is as follows: "In the light of my experience with these two cases of irreducible prolapse, I can state unequivocally that operative intervention should be by means of the abdominal approach, never *per vaginam*, because by the vaginal route the technical difficulties will prove insurmountable" (52).

#### RESULTS

An essential addendum to any operative procedure, particularly one of a reparative or plastic nature, is the periodic observation of the patient at requisite intervals over a sufficient period of time. Without careful examination at follow-up visits and recording of the status, the value of a particular operation cannot be objectively determined. The use of questionnaires to be filled by the patient or of reports submitted by outside physicians not acquainted with the original condition may, in certain types of operations, furnish useful information that might otherwise be unobtainable for such reasons as geographic inaccessibility. It is felt, however, that in the case of vaginal plastic operations, the questionnaire method of follow-up tends to be misleading. Follow-up by questionnaire is necessarily based mainly on functional status as evaluated by the patient, while follow-up by examination also includes objective determination of the anatomic status.

The experience of Lacey (57) is illuminating in this regard. Contact was established by questionnaire with 521 patients; of these, 455 or 87% reported that they were cured. This figure is actually too low, since many, whose replies were unsatisfactory and who failed to appear for further examination, were classified as unsuccessful. Of those who did appear for examination because of suspicion of the possibility of prolapse, a large proportion had symptoms due to other conditions. Shaw (11) also utilized the questionnaire method of follow-up in 549

patients. A patient was considered cured if she stated that she was free from symptoms of "bearing down"; if the reply was unsatisfactory or equivocal, the patient was requested to come for examination. Of this number, 529 or 96% were classified as cured; and 20 or 4% as failures. In this latter group were included 5 who had borne children following the operation, 1 who had a hernia through the vaginal scar, 8 who presented only some laxity of the posterior fornix, and 4 who failed to appear for examination and were classified as failures. As well as could be determined, there was no case of recurrence of the prolapse itself. The slightest degree of recurrence or redundancy of the vaginal tissues was considered an indication of failure; in our opinion, this criterion was too severe.

In this country, Maier and Thudium (10) were able to trace by questionnaires 113 patients out of 138 who were operated on; the majority of these were also examined. There was cure in 111 or 98%. Gordon (7) followed 94 patients (of his series of 152 parametrial fixation operations) by personal examination. There was cure of prolapse in all (including 36 cases of complete prolapse), recurrence of large cystocele in 1, and recurrence of enterocele in 2. He considered recurrent enterocele or large cystocele as evidence of failure; good results were obtained in 91 patients, or 97%. In a subsequent follow-up study of 206 additional patients, prolapse was cured in all but 2 (99%) (8). Included were 26 cases of 3rd degree prolapse, personally observed for long periods of time; all remained cured. Leventhal and Boshes (5) examined 49 of their 51 patients during a follow-up period ranging from 4 months to 2 years. There was cure of prolapse in all but 1 case, or 98%. Recurrent cystocele was found in 8.7%. Follow-up examination in all of Collins' (6) 45 patients during periods ranging from 4 months to 5 years showed that prolapse was cured in all. In 2 cases, there was recurrence of slight relaxation of the posterior vaginal wall; the posterior colporrhaphy was considered at fault here and not the Manchester operations *per se*. In 3 cases, there was similarly a small bulge of the anterior vaginal wall.

Our follow-up system is based on examinations in the follow-up clinic at repeated intervals of (usually) 6 months, after the initial examination 2 to 3 months following operation. Of our series of 722 patients, 57 did not report for examination, in spite of repeated invitations. During follow-up periods ranging from 2 months to more than 10 years, 665 or 92% of our patients were examined (table 12). We believe that this high follow-up rate of ward patients is attributable to three factors: 1) the fact that the vast majority of the patients reside in New York City within easy reach of the hospital; 2) the efficient functioning of the personnel of the follow-up department; and 3) the appreciation by the patients of the interest shown by the examining physicians.

Of these 665 patients, prolapse of the uterus recurred in 7, or 1.05%. In other words, practically 99% of the patients were cured of prolapse. Of these 7 patients, 1 had had 1st degree prolapse (which recurred as 1st degree); 3 had had 2nd degree prolapse (1 recurred as 2nd degree, and 2 as 1st degree); and 3 had had 3rd degree prolapse (all recurred as 1st degree). Three patients were relatively asymptomatic and further operation was not deemed necessary. Parametrial

fixation along with colporrhaphy, was repeated in the other 4 patients, with definitive cure in all. It is interesting to note that there was no recurrence in any of the 41 cases of prolapse of the cervical stump.<sup>2</sup>

Associated vaginal relaxations recurred in 146 cases as follows: 86 cystocele (31 small, 46 moderate, 9 large); 31 rectocele (11 small, 13 moderate, 17 large); 23 cysto-rectocele (6 small, 15 moderate, 2 large); 5 urethrocele; and 1 enterocele. The large majority of these cases were asymptomatic, and certainly would have been overlooked if follow-up had been by the questionnaire method. Persistence or aggravation of symptoms naturally calls for correction. Thus, of these 146 patients, secondary operation was required in only 12 (2 anterior and pos-

TABLE 12

FOLLOW-UP PERIOD	NUMBER
2-6 months	85
6-12 months	72
1-2 years	131
2-3 years	124
3-4 years	91
4-5 years	79
5-6 years	52
6-7 years	21
7-8 years	3
8-9 years	2
9-10 years	1
10-12 years	4
Total .....	665

terior colporrhaphy, 1 anterior colporrhaphy, 2 posterior colporrhaphy, 6 urethroplasty, 1 enterocele repair).

Prolonged follow-up disclosed 8 patients who subsequently required D. and C. for menopausal bleeding, and 6 patients who required hysterectomy (3 fibromyomata, 2 adenomyosis, 1 endometriosis). In addition, we have recently learned from another institution of a patient who underwent total hysterectomy because of fundal carcinoma. (The curettings at the time of parametrial fixation were normal.) It might be argued that if these patients had been subjected originally to vaginal hysterectomy rather than to parametrial fixation, the subsequent procedure would have been avoided. That is true of most of these cases, which represent errors in judgment. As a rule, patients with small, asymptomatic fibroids at or beyond the menopause have been subjected to parametrial fixation rather than vaginal hysterectomy, in the expectation that, with continuing genital involution, future symptoms are unlikely to arise. Our approach has been similar in cases of menometrorrhagia. However, in the presence of symptomatic fibroids prior to the menopause, vaginal hysterectomy (or myomectomy), or

<sup>2</sup> Detailed discussion of the treatment of prolapse of the cervical stump by parametrial fixation is reserved for a separate report from this hospital.

vaginal supravaginal hysterectomy followed by parametrial fixation of the cervical stump is certainly to be preferred.

#### PREGNANCY AND PARTURITION

When the parametrial fixation operation (including cervical amputation) is done during the childbearing period, two questions immediately arise: What is the effect of the operation on future conception, gestation and labor? and, conversely, how does parturition affect the repair?

In reference to the first question, the basic point to be considered is the possible influence of amputation of the cervix, for it is difficult to see how parametrial fixation itself might interfere with pregnancy. Cervical amputation has long been considered inadvisable in younger women where the possibility of future childbearing exists, because of the increased incidence of spontaneous abortion and of cervical dystocia (4, 58, 59). To escape from this dilemma, some operators omit cervical amputation in younger women, while others limit amputation to a very small portion of the cervix. Hunter (59), because of his experience with dystocia following cervical amputation, advocates conservation of the cervix; access to the cardinal ligaments is facilitated by resection of a circular cuff of mucosa above the portio.

From a review of the literature, it is difficult to arrive at an exact idea of the effect of the operation on reduction of fertility. In some series, it is not definitely stated whether cervical amputation is routinely done; in others, the number or percentage of women of childbearing age is not stated; in others, the number of deliveries is mentioned, but not the number of original conceptions, including those that did not proceed to term; and, in still others, it cannot be determined whether tubal ligation was done in some cases, or whether contraception was advised. However, as regards the occurrence of difficulty during labor and the incidence of recurrence following delivery, information is more complete.

In Fothergill's (32) series of 156 cases, 26 women of reproductive age (of whom 23 had had cervical amputation) conceived subsequent to operation. He pointed out that the operation failed to prevent pregnancy in nearly one-quarter of his patients of reproductive age. Two women aborted spontaneously, and 24 women delivered 30 children (23 spontaneous, 7 instrumental). There was no case of obstructed labor. There was 1 recurrence of prolapse in a woman who underwent 3 labors after operation. Lacey's (57) statistics, based mainly on questionnaires, show that, of 521 patients, there were 382 women of childbearing age and 89 deliveries (35 instrumental). There was recurrence in 33.

In Maier and Thudium's (10) series of 113 cases traced by questionnaire, 47 were in the childbearing age. Of these, 12 (of whom 10 had had cervical amputation) became pregnant; 1 aborted and 11 delivered 13 children (10 spontaneous, 3 instrumental). There was no recurrence of prolapse in this group. In Shaw's (11) series of 549 patients, it is not mentioned how many were of childbearing age. Delivery occurred in 27 patients, and recurrence was noted in 5. Labor was normal in 26, and prolonged in 1, presumably (although this is not definitely stated) because of cervical dystocia.



In Gordon's (7) group of 152 patients, 22 were in the childbearing era; 6 patients had 8 deliveries, and 1 patient had 2 abortions. Delivery was normal in all cases except 1, where incision of a rigid cervix was necessary. There were no recurrences. In a later series (8) of 206 cases, 36 were of childbearing age, and parturition subsequently occurred in 10. In 5 of these, no details were available, except that prolapse recurred in 1. Of the other 5, delivery was spontaneous in 1, of low forceps in 3, and by Cesarean section in 1.

Of Leventhal and Boshes (6) series of 51 cases, 18 were of childbearing age; 4 underwent sterilization. One patient had a spontaneous delivery, followed by recurrent cystocele, but without prolapse of the uterus. Collins' (6) group of 45 patients included 9 of childbearing age; none conceived. In Herzfeld and Tod's (60) series of 132 cases, there were 11 deliveries (8 spontaneous, 3 instrumental) without recurrence. In Bazan and Althabe's (61) series of 354 cases, there were 8 deliveries (7 spontaneous, 1 instrumental for a medical indication) without recurrence.

Williams (62) reported 60 pregnancies in 45 women, without recurrence of prolapse. In 37 cases where the cervix had been amputated, pregnancy occurred 49 times (therapeutic abortion 4, spontaneous abortion 20, premature labor 8, term pregnancy 13, still undelivered 4). In 8 cases, where the cervix had not been amputated, pregnancy occurred 11 times (spontaneous abortion 2, term delivery 6, still undelivered 3). This series indicates that cervical amputation increases the incidence of spontaneous abortion and premature labor.

In our series, there were 192 women of childbearing age; tubal ligation was done in 35. Pregnancy occurred in 6 patients, and was interrupted therapeutically in 2. Four patients delivered spontaneously without recurrence.

If we total these series, we find that, of 2989 cases, there were 238 deliveries (instrumental 57, section 1), followed by recurrence of prolapse in 40. This recurrence rate of 16.8% is extremely high; the ineluctable conclusion is that parturition following parametrial fixation greatly predisposes to recurrence of prolapse.

#### COMMENT AND CONCLUSIONS

The parametrial fixation operation presents a number of definite advantages. It is the least radical of the major surgical procedures employed in prolapse, it is technically simple, and facility in its performance is readily acquired. The basic anatomic principles are sound: the operation "preserves a bridge of living and vital tissue across the pelvis from one broad ligament to the other through the cervical stump and uterus, which can be used as a foundation for plastic repair and for support without interruption of the vascular and nutritive channels. The blood supply of all parts which remain is therefore amply preserved, and the possibility of recurrence of prolapse of the vaginal vault and the anterior vaginal wall is thereby reduced" (15).

The operation is entirely extraperitoneal (except when additional procedures, such as tubal ligation, are indicated). Consequently, any postoperative bleeding or inflammatory reaction is confined to the extraperitoneal tissues, and drainage

is external; intraperitoneal inflammatory reaction is usually avoided. Because of the extraperitoneal approach, shock is less likely. The procedure is well tolerated, even by elderly patients. If, for any reason, inhalation anesthesia or spinal analgesia is contraindicated, the operation may be performed without difficulty, with the use of local anesthesia. As has been shown, the incidence of morbidity and mortality is low.

Recurrence of prolapse of the uterus after parametrial fixation is extremely uncommon. (Recurrence of cystocele or rectocele or both is much more common; this, however, does not invalidate the parametrial fixation operation itself.) Among the cases that have constituted strong challenges to the operation are those that had undergone one or more previous unsuccessful operations for prolapse and those that had undergone previous supravaginal or total hysterectomy with resulting prolapse of the cervical stump or vaginal vault. In all cases, the challenge was successfully met. In the rare instances of recurrence of prolapse, repeat parametrial fixation is easily effected and results in definitive cure. As Phaneuf (2) points out, "The advantage of conserving the uterus when operating for prolapse is that if there is recurrence it is much easier to correct with the uterus present than with it removed, for in the latter case the surgeon has to deal with an inverted vaginal vault."

Parametrial fixation is utilizable for all degrees of prolapse, including complete procidentia, although, in the latter, the recurrence rate, small as it is, is, in our experience, greater than in prolapse of lesser degree. We are in complete agreement with Gordon (8), who states that the "Manchester operation is a rational procedure for complete prolapse. . . . The satisfactory end results reported by many operators speak for themselves."

In the younger woman, parametrial fixation has the advantage of conserving menstrual function and reproductive potential. Parametrial fixation (with cervical amputation) probably causes some increase in the incidence of spontaneous abortion, premature labor and cervical dystocia. The recurrence rate, moreover, is greatly increased by parturition. Ideally, in the younger woman with prolapse who desires to complete her family, operation should be delayed, if possible. If symptoms are such that operative correction cannot be postponed, cervical amputation should be minimal. If future pregnancy is not contemplated, tubal ligation may be recommended. Although vaginal delivery is often feasible, Cesarean section is advisable in most cases, particularly if cervical amputation has been high.

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## FIBRO-ADENOMA OF THE OVARY WITH ASCITES AND HYDROTHORAX (MEIGS' SYNDROME)

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The fact that massive pleural effusion and ascites may be associated with benign pelvic tumor is of great significance to the surgeon as well as the internist. It is very probable that, until recently, such a condition remained unrecognized and led to needless fatality in many instances.

Although this condition had been described in 1879, by Cullingworth (1) and in 1906, by Griffith and Williamson, great credit is due to Meigs who, in 1937 in collaboration with Cass (2), emphasized the importance of this syndrome and the greater need for a familiarity with it. Again in 1939 (3), he reported 15 cases from the literature and cited six from a single hospital. To date, more than 75 cases have been reported (personal communication with Meigs).

The occurrence of ascites in a woman over 30 years of age, especially if associated with hydrothorax, might raise the question of several possibilities, such as, congestive heart failure, cirrhosis of the liver, tuberculosis and, above all, malignancy. Most of these would ordinarily offer not too great a problem in diagnosis but the question of malignancy might be more difficult to exclude especially if an abdominal mass could be felt. It is at this point that the possibility of the association of ascites and hydrothorax with a benign tumor of the ovary, and even occasionally of the uterus (4), must be considered. If the patient sees the gynecologist first, the latter might be discouraged by the ascites and the presence of fluid in the chest assuming that the case is one of hopeless malignancy. If, on the other hand, the internist is first to see the case, he may be puzzled as to the etiology and overlook a benign ovarian tumor.

Cullingworth's case died without the benefit of operation and the autopsy revealed a benign ovarian tumor with ascites and hydrothorax that could have been cured by the removal of the tumor. It is quite evident therefore that a knowledge of this association makes the diagnosis relatively simple.

Considerable time, thought and study, has been given to the question of the relationship of the pleural fluid and ascites to this type of tumor. Of all the theories, the most plausible as to the source of the fluid, is that quoted by Rubin (5). i.e. that Spencer and Miller suggested that the ascitic fluid may originate from the tumor itself due to a constant edema from obstruction to the efferent lymphatics in the pedicle. Geibel put the tumors of his two cases into a dry pot; after a few hours the vessel was filled with clear yellowish fluid, the tumor losing  $\frac{1}{3}$  of its weight in 24 hours. Other studies reported by Meigs indicated, on fairly good anatomical grounds, that there were communications between the peritoneal fluid and the pleural lymphatics. The fact that removal of the fluid from one cavity might have no immediate effect on the other, does not disprove this theory,

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for we are not dealing here with large openings, but with small lymphatic communications. This would also explain the failure of air in either cavity finding its way into the other. Two cc. of sterile india ink injected into the peritoneum, was found later in the same concentration in the chest by way of the lymphatics. There was none in the blood right after the peritoneal injection. Further study also revealed that there was chemical identity in both fluids with reference to their total proteins and the electrophoretic distribution of the protein components. Communications were found from abdomen to chest but not from the chest to the abdomen. This was proven by an experiment with particulate matter injected into a dog's abdomen that reached the diaphragmatic lymphatics but did not travel from the chest to the abdomen.

Frequently the patient is aware of the tumor or has been told by a physician that one was present, but when the ascites is very marked the tumor may be masked until enough of the fluid has been removed. The patient usually comes to the physician when she develops dyspnea, abdominal enlargement with a sense of pressure and weight, and weakness, at times she may even look cachectic (fig. 1).

Herriek, Tyson and Watson (6) pointed out that "the syndrome has received infrequent notice in gynecologic literature and none in that of internal medicine. As such cases fall in that "no-man's land" between the internist and the specialist, the significance of the combined thoracic, abdominal and pelvic features may not be appreciated. The result of this is too often the denial of life preserving surgical treatment because of an erroneous diagnosis of inoperable malignant tumor with widespread metastases." They further say: "The importance to the internist, as to the gynecologist, of keeping in mind the fact that a benign tumor may cause hydrothorax as well as ascites, and that the simplest of laparotomies uniformly results in complete relief of the thoracic as well as of the abdominal features of the syndrome, needs general recognition and emphasis." A familiarity with this syndrome leading to recognition and proper management is so rewarding that the report of another case is justified.

#### CASE REPORT

*History.* Mrs. C. C. aged 54 years, white, widow, came to my office on July 14, 1944, complaining of abdominal enlargement and prolapse of the womb. She stated that 4 years previously she had been told by a local physician that she had an abdominal tumor. This was associated with a nervous breakdown at the time. She did nothing further about it but continued at her housework and a job in a pencil factory. About 6 months previously she had noticed that her abdomen was getting larger. In spite of this development she felt quite well and continued to work without interruption. Subsequently she stated that about 4 years ago she had had increased menstrual bleeding with a period of metrorrhagia and that she had been told at that time that she had a pelvic tumor. She also said that in the last 6 months, in spite of the increasing size of her abdomen, she was losing weight and noticed some weakness. There was no shortness of breath, no cough or chest pain, no swelling of the feet or any other complaints. She had one child, no miscarriages or previous operations. She had been separated from her husband for many years. She had had menopause at 40. Either 5 years later or 10 years later, it is not quite clear, she had some staining.

*Examination.* The patient was a poorly developed, emaciated little woman, 4'10" in

height, weighing 122½ pounds, who looked aged and drawn. Her neck veins were full and prominent; there was only partial collapse on inspiration; the thyroid, glands and breasts were negative. On the right side of the chest there was flattening with diminished tactile fremitus and breath sounds all over the back with hyperresonance over the upper lobe anteriorly. There was no displacement of the heart; rate, 110; rhythm, regular; sounds, clear; the pulmonic second was accentuated; the blood pressure was 140 systolic and 86 diastolic. The abdomen was abnormally enlarged and protruding with bulging umbilicus



FIG. 1



FIG. 7

FIG. 1. Lateral view of patient when first seen, July 14, 1944

FIG. 7. Lateral view of the patient 4 years after operation—compare with figure 1

(fig. 1). There was marked venous prominence; the abdomen was soft with signs of a large amount of fluid. Liver and spleen could not be felt. A vaginal examination revealed a complete procidentia with large lateral and posterior ulcerations of the mucous membrane.

*Laboratory Data.* Blood study revealed: hemoglobin, 87%; red blood cells, 4,300,000; white blood cells, 9,050; platelets, 190,000. There was slight anisocytosis. The differential count: polymorphonuclears, 83.5% with juveniles 1.5%; staff, 7%; segmented, 75%; small lymphocytes, 14.5%; large lymphocytes, 2%; mononuclears, none. Sedimentation rate was 18 mm. in 48 minutes. Urinalysis: cloudy; yellow; acid; specific gravity, 1.016; albumin,

trace; sugar, negative. Microscopically, there were many epithelial cells, many leucocytes, an occasional cast, and an occasional red blood cell. The Wassermann test was negative. X-ray of chest (fig. 2) revealed evidence of a large effusion almost completely filling the right chest excepting for a small area over the inner half of the right upper lobe. There appeared to be no displacement of the heart shadow and the left lung was clear excepting for some haziness at the base which might also be due to a little fluid.

*Course.* The impression was: Hydrothorax with ascites probably associated with ovarian tumor (Meigs's Syndrome) and prolapsus uteri. The patient was informed of this diagnosis and surgery was advised. She was referred to Dr. Herman Jaffe who had her admitted to the Greenville Hospital on July 15, 1944.

The right chest was aspirated on four occasions, July 18, 20, 24 and 27, 1944. Various amounts of fluid were removed ranging from 750 cc. on the first occasion to 1000 cc. on the

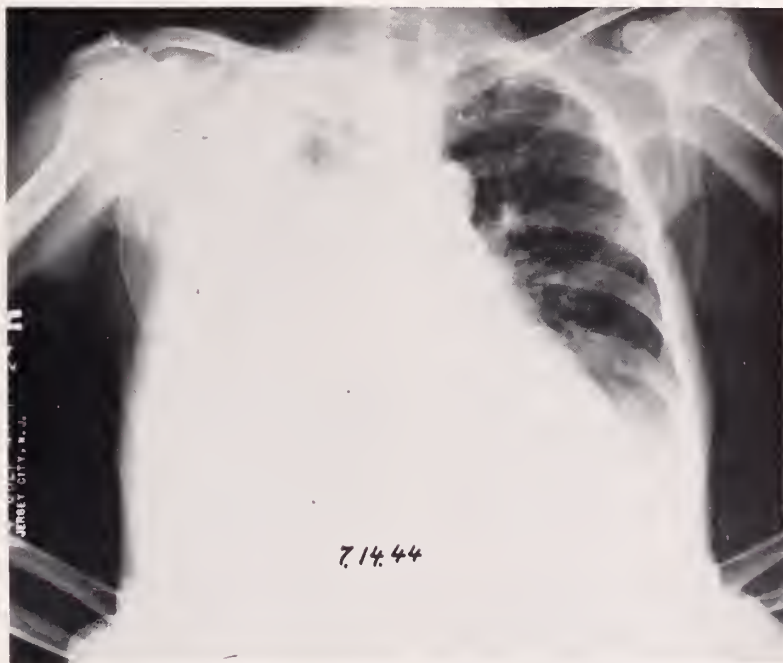


FIG. 2. X-ray of chest when the patient was first seen

second, 750 cc. on the third and 1600 cc. on the last; a total of 3100 cc. The fluid was crystal clear and amber in color. On July 22, 1944, an abdominal paracentesis was done and 8,720 cc. of clear serous fluid were removed. Following the removal of this fluid a large hard nodular mass could be felt in the left iliac region extending to above the umbilicus. It was described as about the size of a "child's football" arising from the pelvis. The upper portion felt nodular. There was no tenderness. The mass appeared to be movable and, in part, cystic. A smaller mass was felt in the pelvis apparently connected with the uterus. The impression was that of a left tubo-ovarian cyst, or myofibroma of uterus. Subsequent examination later in the same day revealed that the mass previously felt in the left side was now in the right iliac region and it appeared to be movable from side to side. The liver edge was palpable and visible a whole hand's breadth below the costal margin. Blood chemistry revealed: sugar, 69 mg%; creatinin, 1.0 mg%; urea nitrogen, 11.2 mg%; total protein, 6.6 mg%; albumin, 4.6 mg%; globulin, 2.0 mg%. After preparatory measures and laboratory observations, a laparotomy was performed on August 1, 1944, under local anesthesia.



*Operation* (by Dr. Herman Jaffe). Under local infiltration with novocaine a 1-3" median sub-umbilical incision was made in the peritoneum. A small niche was made to permit the evacuation of ascitic fluid slowly and controlled by pressure. About one gallon of straw-colored fluid was removed without shock. The incision in the peritoneum was enlarged and a right ovarian cyst was exposed. This was tapped after being surrounded with packings. About one pint of brownish fluid was evacuated without diminishing the size of the tumor mass materially, owing to solid nature of most of the mass. The cyst wall was grasped and removal of the tumor mass started. The upper portion of tumor was markedly nodular and solid but, after some difficulty, the entire mass was evacuated upon the abdominal wall. The mass was the size of a football; nodular at its upper, inner and outer borders, with its lower portion alone having collapsed (cyst). There were no adhesions to the mass. The pedicle was ligated and transfixed and the mass was ablated. The uterus was examined. It was found slightly enlarged and congested. A nodule the size of a plum was embedded in upper posterior wall; it was not disturbed. The left ovary was small and atrophic. Intestinal coils showed no changes on serosa. The abdominal cavity was explored by hand



FIG. 3. Artist's drawing of the tumor mass; it measures 27.5 x 16.5 cm.

and the following information elicited: the liver was enlarged downward 4 fingers below free border. Its surface was not nodular but peritoneal coat was rough, thickened and not smooth—rather verrucous to feel; this was especially prominent on the entire under surface of the liver, especially beneath left lobe. The entire posterior peritoneum of the area on the left side was of same character to palpation—rough, irregular, corrugated and thickened. The rest of the peritoneum of the abdominal cavity was normal. Both kidneys felt normal. The wound was closed in layers.

*Pathological report.* Tissue submitted for study (to Dr. A. J. Gitlitz): ovary and tube (fig. 3).

*Gross description.* The mass of tissue is coarsely nodular and measures 18.5 by 13.5 by 6.5 to 9 cm. in thickness. The serosal aspect is smooth in some places, granular and marked by small, dull, papular excrescences less than 1 mm. in diameter in others. A few portions of the surface are dull and one large area is greenish-yellow and opaque. Within this portion firm foci are present. The mass has been incised. Beneath the green portion there is shaggy, dull, opaque, gray-green amorphous tissue that contains irregular empty loculi. A small amount of yellowish fluid is present in the interstices of the tissue in some areas. Near the junction of the green with adjacent gray tissue in the deeper portions of the mass, the surface is mottled by reddened areas. Opposite the green pole the mass consists of tan-pink, moist, smooth nodules of unequal size with curved borders and gyrated cut surfaces that lie

within white, moist, smooth striated tissue. The central positions of some of the nodules are slightly depressed, white and similar to the surrounding tissue. The fimbriated extremity

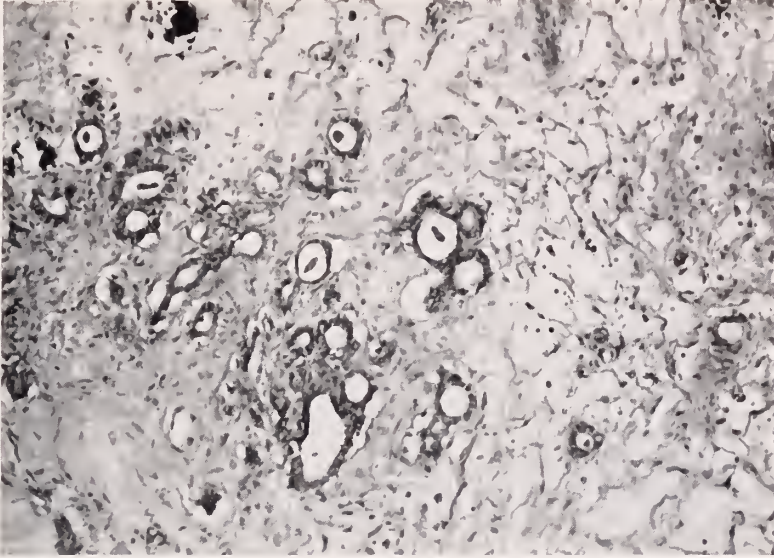


FIG. 4A. Acini lined by cuboidal cells within moderately cellular fibrous stroma. Note the edema and degenerative change of stroma, and the foci of acinar calcification.

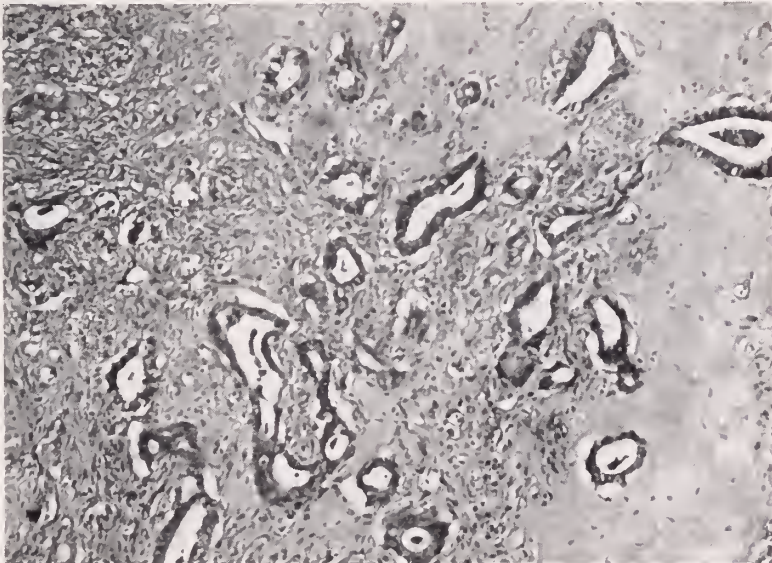


FIG. 4B. More cellular stroma than in Figure A and eosinophilic hyaline change of stroma. Acini are more numerous and show greater distortion of architecture. On higher magnification the acinar lining cells show moderate atypism.

of the tube and the edge of the mesosalpinx are intimately attached to the tumor mass. The fimbriated extremity spreads over a portion of the mass on one side. The lumen is

widely patent and the fimbria themselves reddened and thickened. The tube measures 8.5 cm. in length by 3 mm. in diameter in the isthmic portion and 1 cm. in diameter near the fimbriated extremity. The serosa over this region is covered by translucent gray papules which extend over the mesosalpinx and the adjacent serosal aspect of the tumor mass. The ovary measures 3 x 1.2 x 1 cm. Its surface is covered by pink-gray tissue. The cut surface is firm, pink-white and contains small, white corpora albicantia.

*Microscopic examination.* The mass consists of areas composed of papillary folds lined by cuboidal and columnar epithelium of relatively regular character. Within the stroma adjacent to the papillary areas there are small acini and elongated ones which, in places, are closely set. Some of the epithelial cells present atypical nuclei and mitoses. The entire picture is a relatively regular one. There is extension into the serosa at several points. Portions of the stroma are markedly edematous and degenerated. Some of the acini are

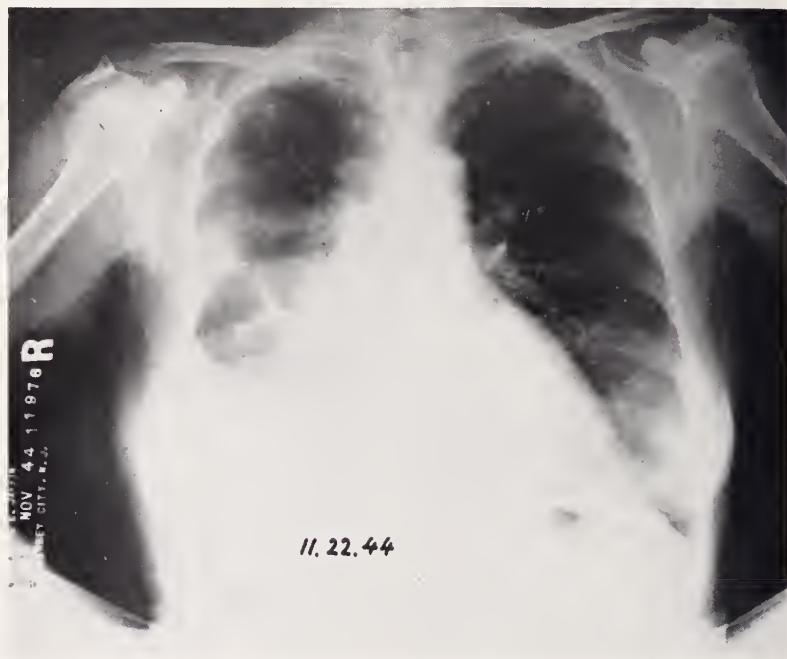


FIG. 5. X-ray of the chest 4 months after operation

calcified. One area of the tumor is necrotic. The ovary is fibrotic and contains corpora albicantia and a small cyst lined by cuboidal epithelium (fig. 4A, B).

*Diagnosis.* Papillary fibro-adenoma (probably of Mullerian duct origin), showing areas of necrosis, foci of calcification, atypism, mitoses and involvement of serosa.

*Course.* The postoperative course was quite smooth and uneventful. The patient was discharged on the 15th day after operation, wound having healed by primary union. Upon discharge her general condition was good. There was still a slight enlargement of the abdomen due to a small amount of fluid. The right chest still showed a small residue. She was seen again on September 20, 1944. At this time her weight was only 104 pounds, her blood pressure 150 systolic and 90 diastolic. Her pulse was still rapid, 112. She looked and felt well. The veins of the neck, while still full, in the supine position now showed good inspirational collapse. There was still some dullness at the right base in front and behind with diminished breath sounds. Tactile fremitus was present. The abdomen was now flat. There



was a long midline scar from the operation and some umbilical hernia. Abdomen felt rather "doughy." There was no hernia. The liver surface felt smooth. Spleen was not felt. The extremities showed no edema. A vaginal examination now revealed a complete disappearance of the previous procidentia with only a first degree of prolapse. Bimanual examination was negative excepting for some fresh bleeding. Fluoroscopy showed there was little clouding at the right base with obliteration of the costophrenic angle.



FIG. 6. X-ray of chest, lateral view 4 months after operation

She was seen again November 22, 1944, reporting that she felt fine. Her general appearance was good. She now weighed 117 lbs. and there was still diminished resonance at the right base, though less than previously. The abdomen was rather prominent but tympanitic; scar was firm; the liver could not be felt. X-ray at this time (figs. 5 and 6) showed further absorption of previous exudate with increased aeration of the right lung. Sedimentation time was normal.

The patient was last seen in September, 1948, when she reported that she had been working uninterruptedly since October, 1944. She looked remarkably well (fig. 7) excepting that



she was much over weight (152 lbs.). Examination of the chest was negative excepting for a few crepitant rales at the right base. X-ray study of the chest revealed the lungs clear excepting for slight clouding above the right diaphragm (fig. 8).

In a letter dated March 26, 1950, she stated that she was "feeling fine, in the best of health, and working every day."



FIG. 8. Chest findings (9/27/48). Note marked clearing of right lung as compared with the original findings, and only slight residual pleural changes.

#### CONCLUSIONS

1. Case of ovarian fibroma with hydrothorax and ascites cured by surgical removal of the tumor with a six year follow-up is reported.
2. The existence of this syndrome should be known to internist and surgeon.
3. The disappearance of ascites and hydrothorax after removal of the ovarian tumor established the latter as a definite etiologic factor.

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## TORSION OF THE FALLOPIAN TUBE PRODUCING GANGRENE OF THE SMALL INTESTINE\*

LOUIS BURKE, M.D., ARTHUR N. DAVIDS,† M.D., AND GABRIEL SELEY, M.D.

Torsion of the Fallopian tube with the subsequent creation of an acute abdomen used to be considered an exceedingly rare condition (1). There is apparently an increasing awareness of this entity since more cases are being reported in the literature. This is especially true of the French observers who consider torsion of the "normal" tube a definite, established, clinical and pathological entity that occurs more frequently than usually supposed (2-5).

Since the first reported surgical case of torsion of the Fallopian tube by Bland-Sutton in 1890 (6), there have been several comprehensive reviews on the subject (1, 7, 10). Sharp distinction is made between torsions of the vaginal tube and torsions of the tube in married women (1, 10). The occurrence of the former is more uncommon than the latter. It is felt that beyond the state of virginity and following abortions and pregnancies, there are too many possibilities for infection and mechanical derangements which may leave an affect on the structure and function of the tube. Anspach (7) and Thorek (11) are of the opinion that torsion of a normal tube is impossible and that in the case of torsion in which the tube appears to be normal, the condition is the result of an unrecognized salpingitis with hydrosalpinx following an acute exanthema, vulvovaginitis or an attenuated tuberculosis in childhood.

Although the literature contains instances in which the occurrence of peritonitis or associated appendicitis together with or secondary to torsion of the Fallopian tube has been noted, there have been no cases reported of acute gangrene of the bowel secondary to torsion of the adnexa. Because of the relative infrequency of torsion of the Fallopian tube, and because of this most rare complication, the following case is presented.

### CASE REPORT

*History* (Adm. #609457): Mrs. H., aged 47 years, gravida 2, para 2, divorcee, entered the Mount Sinai hospital on March 29, 1950, complaining of abdominal pain of 24 hours duration. She had the usual childhood diseases of measles, mumps and chickenpox; otherwise she was well all her life. She never had diphtheria or scarlet fever. Twenty-four hours prior to admission, she experienced severe, crampy, lower lumbar pain, lasting five minutes, associated with crampy pain in both lower quadrants of the abdomen. The interval between cramps was about one half hour and severe aching constant pain was present during this time. At the onset, the pain was associated with nausea and vomiting. The pain continued up to the time of admission and she continued to have bouts of retching without bringing up any intestinal contents. There was no diarrhea. The patient had had a bowel movement the day before admission. There were no dysuria, frequency or hematuria.

*Menstrual History.* The patient had had two full term deliveries in 1921 and 1925, and a

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four month abortion in 1936. Her menses started at 13 years of age, occurred every 28 days, and lasted 4 days. For the past two years the cycle had been very irregular, bleeding occurring once every 6 to 7 months. The last period occurred six months prior to admission.

*Examination.* The patient was in acute distress complaining of severe pain and writhing in bed, with her knees flexed. Her temperature was 99.8°F.; pulse, 92 and the blood pressure 128 systolic and 72 diastolic, the heart and lungs were normal. There was marked spasm and tenderness in the lower abdomen, especially on the right side; rebound tenderness was present. There was no abdominal distension and no masses could be palpated. Pelvic examination revealed a parous, clean vulva and vagina. The cervix pointed posteriorly. There was marked tenderness, especially on the right, on movement of the cervix. The uterus was not made out because of the marked abdominal spasm. The right adnexal region contained

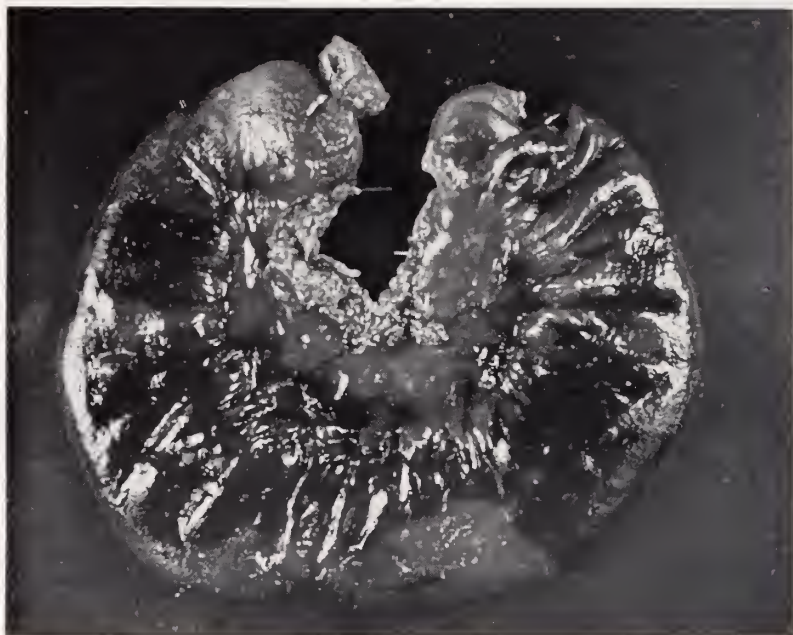


FIG. 1. Specimen 1 of gangrenous ileum removed at operation

a very tender, cystic mass, which on recto-vaginal examination was seen to fill the posterior cul-de-sac.

*Laboratory data.* Catheterized specimen of urine revealed 1-2 red blood cells per high power field. Sedimentation rate was 7 mm. in one hour; Hemoglobin, 13 grams; White blood count, 17,500 with 71% segmented and 19% non-segmented polymorphonuclear leucocytes, 7% lymphocytes, 3% monocytes and toxic granulations.

*Course.* The patient's abdomen became more rigid and her temperature rose to 101°F. while she was being prepared for operation. The preoperative diagnosis was either twisted ovarian cyst or acute appendicitis in close proximity to an ovarian cyst. On the afternoon of admission she was explored. Inspection of the pelvis revealed a loop of gangrenous terminal ileum. This loop of bowel could not be delivered from the pelvis. On further investigation, a tight ring could be palpated which completely surrounded the loop of bowel. The proximal segment was slightly dilated and the distal portion collapsed. The ring was made by the Fallopian tube which had twisted upon itself from right to left and had also become looped so that the fimbriated end of the tube had become adherent to the uterus close to the isthmus of the tube. The tube was doubly clamped and divided releasing the incarcerated intestine. The loop of bowel and its mesentery were not twisted, but the bowel was black in

color. The involved segment measured 28 cms. The pelvis contained a small amount of foul smelling free fluid. The mesentery of this part of the bowel was thickened, the vessels congested and there were a number of ecchymotic spots present. The involved segment was excised and a side to side entero-enterostomy performed. The stump of the tube was re-peritonized by approximating the round ligament to the uterus. The wound was closed in layers, with wire sutures being used for the fascia.

*Pathologic examination* (#104747) revealed a segment of small bowel showing hemorrhagic infarction with viable bowel at both ends of the resection (fig. 1). There was no evidence of diffuse vascular disease. Acute inflammation of the peritoneal surfaces was present.

#### DISCUSSION

There have been many theories proposed to explain torsion of the Fallopian tube. These may be summarized:

1. *Anatomic Theory.* The tube and ovary are extremely mobile organs. The tube usually falls medialwards and posterior producing a twist of some  $90^\circ$  in itself. Any increase in the contents of the lumen, or displacement of the uterus would tend to increase the angulation of the tube.<sup>8</sup> The peristaltic motion in the sigmoid, cecum or neighboring loops of ileum would also tend to alter its position. An abnormally long mesosalpinx would also favor the production of this entity (13).

2. *Hemodynamic Theory.* Thorek (11) called attention to the fact that the vessels in the mesosalpinx are tortuous, with the veins being more flexible than the arteries. Thus unequal changes in pressure in these vessels caused them to assume a spiral course and favored torsion. That this can occur was experimentally demonstrated by Payr (14) who produced torsion of the spleen, when fluid, under uniform pressure, was forced through the artery and veins of a spleen suspended by its pedicle.

3. *Selheim's Theory.* Selheim (15) was of the opinion that visceral torsion was due to the transformation of the movements of the body on internal organs due to sudden changes, stoppage, or external violence.

4. *Physiologic Theory.* In view of the known fact that the tube manifests physiologic peristalsis, disturbances of these movements are considered by some to be a factor in the production of torsion (16).

5. *Vulvovaginitis Theory.* Anspach (7) and Norris (17) attach importance to the occurrence of vulvovaginitis secondary to childhood exanthemata. They feel that the whole genital tract may be involved, producing salpingitis and a hydrosalpinx which later in life may grossly appear normal.

Kustner's law (18), to the effect that right sided adnexa twist from right to left and those of the left side from left to right has proved true in the majority of cases reported. Anspach (7), Regad (16), and Smith and Butler (19) reported that the twists occur on the right side three times as frequent as the left. Several reasons have been offered to explain this:

1. The sigmoid colon on the left tends to prevent movement of the left adnexa (1).

2. Peristaltic activity of the small intestine tends to be more located on the right (1).



3. Spastic contractions of the cecum affect the right adnexa, favoring torsion.

4. The nearness of the appendix on the right, with adhesions due to inflammation favors the torsion of the right adnexa (11).

In the case herein reported, probably several of the above factors played a role in the looping and torsion of the tube. It is not without significance that not only did the tube undergo torsion, but it also looped itself and the fimbriated end became adherent to the uterus. It is conceivable that this occurred at childhood as the result of a vulvovaginitis, or after her pregnancies or abortion. With the presence of a loop, a segment of ileum slipped through and became strangulated, similar to an internal hernia of the mesentery. Whether torsion occurred as the loop was formed, or vice-versa, can not be determined.

The frequency with which symptoms of tubal torsion simulate lesions of the appendix or twisted ovarian cyst makes this mistake in diagnosis a frequent one; as was done in the case reported. In retrospect, there are several features of the case which fit in with the syndrome described by the French clinicians, who claim to have diagnosed it pre-operatively. These are:

1. Acute sudden onset of pelvic pain with agitation and anguish. The pain may be dull and aching with exacerbations, or may be short, sharp and agonizing resembling renal colic.

2. At onset, there usually is a mild tachycardia, with a nearly normal temperature. Later the fever rises.

3. Vomiting at the onset of symptoms.

4. The presence of a palpable mass, lateral and posterior to the uterus, of irregular consistency, extremely tender and no pathognomonic signs of ectopic pregnancy.

With the foregoing in mind, the condition should be thought of with all other causes of an acute abdomen, such as appendicitis, intestinal obstruction, ectopic pregnancy etc., and operation performed as quickly as possible.

#### SUMMARY

1. An unusual case of acute gangrene of the terminal ileum due to torsion and looping of the right Fallopian tube is presented.

2. Possible factors in the etiology and symptomatology are discussed.

3. Torsion of the Fallopian tube is an established clinical and pathological entity, and must be considered in cases of acute surgical abdomens.

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# CESARIAN SECTION AFTER COLECTOMY FOR ULCERATIVE COLITIS

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Pregnancy in patients with ulcerative colitis is not unusual. Authorities in the field have expressed diverse opinions concerning the effect of pregnancy on the disease. Boekus (1) mentions the possible adverse effect of gestation on colitis patients. Crohn (2) also stresses the strong probability of a flare-up of colitis symptoms, particularly after pregnancy. He emphasizes the marked influence of emotional tension on the symptoms produced. Crohn distinguishes sharply between ileitis, which is curable by surgery—either by resection or short-circuiting—and colitis, in which a “cure” is rarely claimed. He advises careful consideration before marriage and even greater caution before a pregnancy is contemplated in a patient with ulcerative colitis.

Garlock (3, 4, 5) has written extensively concerning the surgical management of patients with intractable ulcerative colitis. More recently McKittrick and Moore (6) have evaluated ileostomy in the management of colitis patients where medical treatment has failed. They report a patient who had two successful pelvic deliveries despite ileostomy and colectomy.

The following case is described because it appears to be exceptional, since the literature fails to reveal any instance of a patient with severe ulcerative colitis, treated by colectomy, and subsequently delivered by cesarian section.

## CASE REPORT

*History.* Mrs. B. S. was first admitted to The Mount Sinai Hospital, on November 22, 1938. She was then aged twenty-four years and gave a two-year history of symptoms typical of ulcerative colitis. She had experienced anorexia, nausea, vomiting, lower abdominal pain, and diarrhea, having lost twenty pounds in the two months prior to admission. An anal fistula was excised and revealed “chronic nonspecific inflammation with no evidence of tuberculosis”. Barium enema revealed severe ulcerative colitis extending from the cecum to the region of the sigmoid. In spite of intensive medical therapy the patient continued to have fever, diarrhea, and loss of weight and was sustained by repeated blood transfusions. Examination of the rectum and lower sigmoid indicated that they were not involved. Therefore it was decided to perform an ileo-proctostomy rather than an ileostomy. This was carried out by Dr. John H. Garlock on January 16, 1939, as a preliminary procedure to colectomy.

Following this operation the patient improved markedly, and gained twenty-seven pounds. Eight months later, on October 13, 1939, a left hemi-colectomy was performed with resection of the sigmoid, descending colon, and the left half of the transverse colon. She continued to do well, and on November 29, 1939 a right hemi-colectomy was performed. The pathological report was “acute and chronic ulcerative colitis”.

During the next three years the patient did very well. She gained weight, and

had not more than four or five stools daily without bleeding. She then married, and expressed a desire to have a child. Because she had done so well following surgery it was considered safe for her to conceive.

Approximately four years after the colectomy she became pregnant without delay, her last menstrual period occurred on October 17, 1943. She passed through an uneventful pregnancy, gained twenty pounds, maintained a normal blood pressure throughout, and disclosed no albuminuria. She averaged two to three semi-soft stools per day with no pus, blood, or mucus, and had no abdominal cramps. It was decided, in spite of her normal gynecoid pelvis, to deliver this patient by elective cesarian section because vaginal delivery might traumatize the anastomosis deep in the pelvis. Two weeks before her expected date of confinement, the patient ruptured membranes spontaneously with the vertex unengaged. A typical low-flap cesarian section was performed. The abdomen was entered through a left paramedian suprapubic incision, practically no adhesions were encountered, and the operation was completed without difficulty. A normal healthy six and one-half pound female child was delivered. Post-operative convalescence was uneventful, the wound healed by primary union, and the patient was discharged on the eleventh day.

There were no colitic symptoms for eight months. Then, and the patient herself emphasized the effect of emotional tension, the combination of worry about her baby and difficulties at home caused her to be "very much upset". She again began to have abdominal cramps, fever and diarrhea. She lost twenty-five pounds and was re-admitted to the hospital on November 27, 1946. She responded fairly well to medical treatment.

She reentered the hospital June 3, 1948, and remained there more than one year. During this time she developed inguinal, ischio-rectal, and peri-anal abscesses. Numerous incisions were required and the patient developed a fistula in the abdominal wall at the site of an abscess, and also several peri-anal fistulae. Because of the persistence of her symptoms it was decided to perform an ileostomy. This was done on October 7, 1948. In spite of this procedure, the peri-anal fistulae continued to drain, and on inspection the rectal mucosa was found to be "ulcerated and covered with purulent exudate". For this reason an abdomino-perineal resection for ulcerative proctitis was finally done. The patient made a good recovery. Her ileostomy is now functioning well. She has gained back all the weight she had previously lost, and reports her general condition as "excellent".

#### SUMMARY

A patient with extensive ulcerative colitis failed to respond to medical treatment. There was marked involvement of the entire colon, but the rectum and lower sigmoid were free of disease. For this reason ileo-proctostomy rather than ileostomy was performed, followed by a two-stage colectomy. She improved so remarkably that she subsequently married and was allowed to have a child. She went through an uneventful pregnancy and was delivered by cesarian section. Eight months later she had a severe recurrence of her colitis symptoms. Her



course then was characterized by multiple pelvic and peri-anal abscesses and fistulas necessitating ileostomy and finally abdomino-perineal resection because of residual proctitis.

This case is of interest because it demonstrates that the patient responded to carefully planned surgical treatment when medical measures failed. However, there was a recurrence of colitis, apparently due to the stress of motherhood. This is in keeping with the warning of Crohn (2) who believes that ulcerative colitis patients do poorly following marriage and pregnancy. This patient, whose colon already had been removed, developed such severe symptoms that further surgery was required.

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## ENDOMETRIOSIS IN A LAPAROTOMY SCAR

### REPORT OF A CASE WITH UTERO-ABDOMINAL FISTULA\*

NATHAN MINTZ, M.D. AND JOSEPH A. GAINES, M.D.

The growth of aberrant or ectopic endometrium in or about the pelvic structures is far more common than is generally supposed. Among careful observers it has been found in as high as 43 per cent of all gynecological laparotomies. To the gynecologist endometriosis is of paramount importance not only because of its frequency, but also because of its widespread distribution, and its protean manifestations. Its occurrence in young women particularly makes it a constant challenge to the surgeon's ingenuity and ability in his desire to preserve ovarian and child-bearing function.

The sites in which endometriosis has been encountered include the uterus, ovary, fallopian tubes, peritoneum, large and small intestine, appendix, recto-vaginal septum, bladder, round and inguinal ligaments, umbilicus, vagina, vulva, and laparotomy scars. Its occurrence within an incisional scar of the abdominal wall was first described by Robert Meyer in 1903 (1). Our records at this hospital disclose only five such cases during the past twenty five years. Because of its rarity, interesting pathogenesis, and possible prophylaxis, a case with utero-abdominal fistula is described and discussed.

#### CASE REPORT

*History.* M. W., aged 29 years, gravida 2, para 2, entered for the first time the Gynecological Service of The Mount Sinai Hospital in October of 1938, because of menorrhagia of two years duration. Pelvic examination revealed a uterus enlarged by multiple fibromyomata to the size of a three and a half months gestation. Because of the patient's youth and desire for more children a multiple myomectomy was performed. Fourteen fibroid tumors of varying size were enucleated. The endometrial cavity was not entered. The post-operative course was moderately febrile for three weeks. At the time of discharge from the hospital on the 27th postoperative day the wound was healed except for a small collection of serum at the lower angle. The uterus was found to be the size of a six weeks gravidity, slightly irregular in contour, movable, and not unduly tender. Seven months after the operation the patient first experienced pain in the region of the abdominal incision during a menstrual period. This recurred periodically during subsequent menses. Four months later a tender lump was noted in the lower angle of the scar which increased in size with each catamenia. In January 1940, 14 months after the operation, a discharge of blood from the scar tumescence was first apparent. During the following three months, until the patient was readmitted, each menstrual period was accompanied by localized pain and bleeding from the tender swelling within the laparotomy scar.

*Examination* revealed a healed hypogastric left paramedian incision. Near the lower angle, a peach size, firm, tender, poorly demarcated mass could be felt. This was adherent to the overlying skin and to the deeper structures of the abdominal wall. A small dimple was noted but it could not be probed easily. On pelvic examination the cervix was lacerated but clean. The body of the uterus was slightly enlarged, symmetrical, anteflexed, and apparently fixed to the anterior abdominal wall. Attempted motion of the uterus was moderately painful. The adnexae could not be distinguished.

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\* From the Gynecological Service of The Mount Sinai Hospital, New York.



FIG. 1. Utero-Abdominal fistula: Excised specimen ( $\frac{2}{3}$  actual size) showing skin, subcutaneous tissue and fistulous tract. The latter has been opened longitudinally and ends in a small segment of uterine wall.

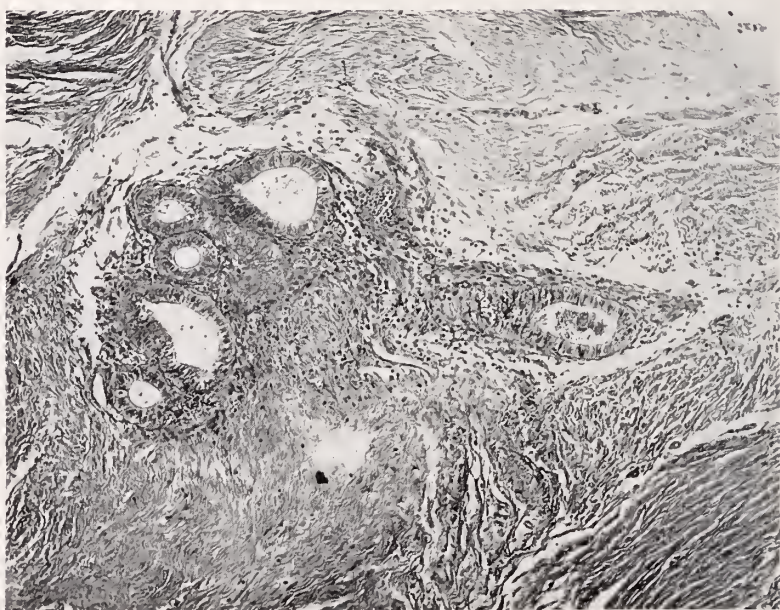


FIG. 2. Endometrioma of abdominal scar (low power) showing a nest of endometrial glands surrounded by endometrial stroma and fibrous tissue.



*Operation.* A pre-operative diagnosis of endometrioma of the abdominal wall was made. An elliptical incision was made about the scar, care being taken to go well beyond the limits of the mass. The rectus fascia was then exposed and split and the mass found to extend through the rectus muscle down to the peritoneum. The latter was likewise incised, and after dissecting away numerous adhesions a tubular tract about the thickness of a finger was discovered extending from the abdominal wall to the uterine fundus. Because of the intimate fusion of this tract to the uterus it was necessary to excise a wedge shaped segment of the uterine wall down to and including the endometrium in order to be sure that the tract was excised in its entirety. The uterus was closed with two rows of interrupted chromic sutures. Pelvic exploration revealed no other abnormalities. The abdominal wall was then closed in layers.

*Pathological findings.* "The specimen consists of an ovoid mass measuring 6 x 4 cm., with an overlying elliptical segment of skin 12 cm. long (fig. 1). A linear scar extends along



FIG. 3. Cross section of fistulous tract (low power) showing an epithelial lining and stroma similar to that of the endometrial cavity of the uterus.

the entire length of the skin and ends in a distinct dimple-like retraction. The tissue is firm and rather shotty. On section there is a marked amount of searring with numerous minute bluish cyst-like areas. Running through the center of the mass is a well defined tract, the inner lining of which is smooth and glistening. It extends from the skin to a wedge-shaped segment of uterine muscle.

Microscopically the tumor mass is composed of a considerable amount of fibrous tissue in which are embedded numerous nests of endometrial glands. Most of these areas show the glands to be surrounded by typical endometrial stroma (fig. 2). The glands are of varying size. Some are lined by flattened or disrupted epithelium; others by an active proliferating epithelium. Occasional glands are filled with blood. The fibrous tissue is quite dense. In a few areas there are collections of fibroblasts and macrophages, the latter containing the characteristically coarse hemosiderin pigment.

Cross-section through the fistulous tract reveals an inner lining of epithelium analogous to that of the endometrial cavity of the uterus, including cilia (fig 3). A fairly compact



stroma surrounds the epithelium. The remainder of the tract is composed of fibrous tissue. The wedge shaped segment of uterus resected with the specimen shows several areas of adenomyosis and an endometrial lining in the proliferative phase."

*Course.* The postoperative course was entirely uneventful. At the time of discharge from the hospital on the eighth day, the wound had healed by primary union. The patient was seen at intervals during the next seven years and has remained perfectly well. There has been no recurrence of the mass in the abdominal scar and the uterus has not grown appreciably in size.

#### COMMENT

Scar endometriosis has been known to follow Caesarean section, hysterotomy, myomectomy, salpingectomy for tubal or ovarian disease or ectopic pregnancy, tubal ligation, and particularly ventrofixation of the uterus to the abdominal wall. Occasional instances have been described after appendectomy or inguinal hernioplasty. In a review of the world literature up to 1929 Hosoi and Meeker (2) collected 87 cases of scar endometriosis of which approximately 63 per cent were preceded by an operation on the uterus, 23 per cent on the tube, and 14 per cent by miscellaneous procedures, including appendectomy. In their series there were seven proven cases of uterine fistula. In 1941 Wyrens and Randall (3) reported 31 cases, 74 per cent of which were preceded by some form of uterine operation. Communication between endometriosis of an abdominal scar and a tubal stump or the uterine cavity through an intermediary fistulous tract has been demonstrated by Sampson (4), not only by careful gross and microscopic study, but also by the injection of pigmented gelatin under pressure into the uterine cavity of totally resected specimens. Attempts to estimate from the literature the percentage of cases associated with communicating fistulae is difficult because in many instances the peritoneal cavity was not explored. The pathogenesis of scar endometriosis is still a matter of speculation. Sutton (5) mentions five ways in which theoretically the abdominal scar may become the seat of endometrial invasion; 1) direct outgrowth of mucosa from a tubal stump, 2) a direct outgrowth of endometrial mucosa through a wound of the uterine cavity, 3) contamination of the abdominal wound by bits of mucosa set free during the course of an operation on the pelvic organs, 4) invasion of the peritoneal under-surface of an abdominal scar by bits of endometrial tissue set free in the abdominal cavity and 5) serosal metaplasia. Ballin (6) has proposed the term "menstrual fistula" to describe the periodic discharge of blood from a laparotomy scar at the time of the menses. He includes those cases in which there is a simple enclosure of endometrial tissue in the postoperative scar. Perhaps the term may be more properly reserved for those instances in which a tract can be demonstrated between the uterus or tube and the abdominal wall.

The symptoms and signs of scar endometriosis may first become apparent within a short time or several years after operation. Usually they begin during the first year. A firm, fixed, tender nodule is noted in any or all layers of the abdominal wall about the laparotomy scar. This increases in size as the endometrioma spreads. Pain and tenderness are manifest especially at the menses. The mass may show a bluish discoloration and finally perforate through the skin,

with the discharge of menstrual blood at each period. The sinus tract may end in the abdominal wall or continue as a fistula to the uterus or tubal stump.

The treatment of scar endometriosis depends upon the extent of involvement of the abdominal wall, the patient's age, the necessity for preserving menstrual, ovarian or child-bearing function, and the type of operation previously done. If the endometriosis is localized to the abdominal scar, simple excision may suffice. If the scar endometriosis is densely agglutinated to the pelvic organs, with a fistulous communication, a hysterectomy and bilateral oophorectomy is often necessary. At times, as illustrated by the case above, one may be more conservative. If the abdominal wall is widely involved the resulting deficit may be difficult to close. Under certain circumstances X-ray castration may be utilized.

#### SUMMARY

A case of scar endometriosis with utero-abdominal fistula is described, and the general features of this entity are discussed.

A study of the incidence and pathogenesis has suggested to us that certain precautions may be advantageous in the prophylaxis of scar endometriosis:

1. Pelvic operations should not be undertaken, if possible, during or immediately after the menses. It is at this time that menstrual blood is not infrequently seen within the posterior *cul-de-sac*.

2. The abdominal wall should be carefully shielded whenever the tubal or uterine cavity is entered.

3. Uterine incisions should be carefully peritonealized.

4. When salpingectomy is done the proximal end of the tube should be excised well into the cornu to avoid tubal stumps.

5. The ventro-fixation operation should not be performed.

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# RECURRENT CERVICAL METASTATIC CANCER

## TWO CASE REPORTS

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Most cancers which arise in the mouth metastasize to the neck, but they rarely descend below the clavicle. In the neck, the aggressiveness of the local spread varies, and is often unpredictable. Occasionally a primary cancer in the oral-pharyngeal region may remain so small as to be unrecognizable with the unaided eye, and yet give rise to multiple and bulky tumors on both sides of the neck (1).

Sometimes the primary growth in the mouth or lip may be controlled while the metastatic lesion grows in a slow, persistent or recurrent fashion in the neck; seemingly defying therapeutic efforts, it nevertheless remains local in the neck for a long time. In such cases, persistency and boldness with retrial of radical or local re-operation or localized irradiation may have their reward. As long as the primary growth in the mouth is controlled, and the mass in the neck is not entirely fixed and immobile, and has not spread below the clavicle, it is not entirely hopeless. The degree of fixation which precludes operation varies with the individual surgeon, and naturally is subject to individual opinion. A small residual mass of cancer, which could not be removed surgically, may be sterilized with radon implants or treated intensively with locally destructive X-ray therapy (2). At any rate, with modern anesthesia and the availability of large quantities of blood, many cases which heretofore were considered hopeless and were relegated to custodial care, are no longer in such a category.

I wish to report two cases to illustrate the above principle, i.e. if the primary lesion in the mouth is arrested, and the disease in the neck is still local, persistent effort at its eradication should be encouraged and will not be unrewarded. Although the follow-up in these 2 cases is not too long (3 years and 2 years respectively), we think the results so far have justified the above statement.<sup>1</sup>

## CASE REPORTS

*Case 1. History.* Mrs. A. B., aged 53 years, was first seen on April 10, 1947. The patient said that she had had a small ulcer on the right side of the tongue for three years. A biopsy was taken in October 1945, and since then, she thought, the lesion grew larger. A wide local exsision of the lesion had then been done in May 1946; it healed well. In June 1946 she received a series of X-ray treatments to the right side of the neck. She first noticed a node in the right side of the neck about 2 months after the operation, and 2 months after the X-ray treatments she noticed a swelling appear again in her neck. A neck dissection had then been done on December 27, 1946. The surgeon's operative notes, which he kindly made

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<sup>1</sup> The question as to which of such cases should have only a radical neck dissection, and which should have a radical neck dissection with a hemimandibulectomy and exsision of the local growth in the mouth in continuity in one stage did not have to be considered here, since in both instances the primary neoplasm was controlled. The indications for this operation will require a few years more to determine.

available to me, indicated a fairly complete dissection.<sup>2</sup> She convalesced satisfactorily from this neck operation, but 3 months later (March 1947, 1 month before she was first seen by me), she again noted an enlarged nodule in the neck.

*Examination.* The patient was a somewhat frail and slightly anemic woman. Her general physical state was quite satisfactory. The tongue showed a healed sear on the right lateral posterior portion without induration or ulceration. The right side of the neck exhibited the scars of the previous operations, and some brownish pigmentation of the skin from the X-ray therapy. There was a mass behind the angle and ascending ramus of the right mandible. It was elevated, about 3 centimeters in diameter, and there were two draining sinuses in its upper portion. There was some fixation to the deep structures of the neck, but it was still somewhat movable, both laterally and vertically. There was considerable induration in the skin and subcutaneous tissues between the upper portion of the mass and the mastoid eminence, and some fixation in the depth in this region. The stump of the sternomastoid muscle could be felt above the clavicle. The supraclavicular triangle was full, and evidently the contents still remained, but there were no nodes palpable.

*Course.* The patient was apparently in general good health, and the mass, although fixed, was still local. Although there was induration immediately underneath the mastoid process, the disease apparently had not invaded the lower triangle of the neck, and it was radiation-resistant. It was then decided to attempt a radical neck dissection; this was done on April 16, 1947. The incisions circumscribed a wide area of skin, fully 3 inches long by 2 inches wide, and extending from the region of the mastoid eminence to the mid-sternomastoid region. This contained the sinuses and indurated thickened tissue, all of which was removed with the specimen. A complete block dissection of the right side of the neck was then done. The stump of the sternomastoid and the jugular were divided close to the clavicle. These regions were rather glazed and fibrous because of the previous X-ray therapy. The mass was dissected up from the lower portion of the neck. The supra-clavicular triangle was cleared with relative ease. At the level of the hyoid region, however, there was dense infiltration with the malignant tissue. It had become intimately attached to the sheath of the carotid at about the point of bifurcation. Separation here was quite difficult, and at this point the growth had to be cut through to clear the sheath of the carotid artery. A biopsy taken from the adventitious tissue of the wall of the carotid artery which was left, showed, on microscopic examination, definite carcinoma (fig. 1). A small fragment of the growth was spilled at this point. The hypoglossal nerve passed directly through the growth, and had to be sacrificed. The dissection was continued upward, and the upper portion of the jugular region up to the mastoid eminence was cleared in typical fashion. Three days later a skin graft about 3 inches in diameter was applied.

She convalesced satisfactorily and left the hospital on the eleventh post-operative day.

Two months later a progress note dated June 24, 1947, read as follows: "definite recurrence is noted in the upper border of skin graft sear below the angle of the mandible. This is near the spot on the sheath of the carotid artery which was involved in the residual carcinoma. Also, there are two suspicious indurated areas fully 1 centimeter from the posterior margin of the graft underneath the skin. This is over the trapezius muscle and the posterior portion of the neck."

On August 3, 1947, radon seeds were inserted into the area overlying the region of the carotid bulb and also into the recurrence in the posterior portion of the neck.

In September 1947, the area overlying the carotid was slowly healing, however, posteriorly in the region of the trapezius the ulcer was spreading and was now an indolent

<sup>2</sup> "Flaps dissected back; the sternomastoid was cut loose from the clavicle, the internal jugular divided, the dissection carried upward removing all of the sternomastoid, the jugular vein, portions of the straight muscles. The upper end of the sternomastoid was cut across one inch below the mastoid process. The tip of the parotid gland was removed, submental nodes were removed. There was a hard metastatic node near the upper border of the sternomastoid, from which some whitish cheesy cellular material escaped".



necrotic ulcer 2 centimeters in diameter with some induration about it (fig. 2). Three radon seeds were again placed here, after thorough cauterization. Apparently at this stage there was no cancer in the neck grossly, except the ulcer in the posterior portion overlying the muscle. Since there were no vital structures immediately below this, and since it had not responded to further radon and cautery destruction, it was thought worthwhile to widely excise this mass with the underlying trapezius muscle. This was done on September 19, 1947, under local anesthesia.

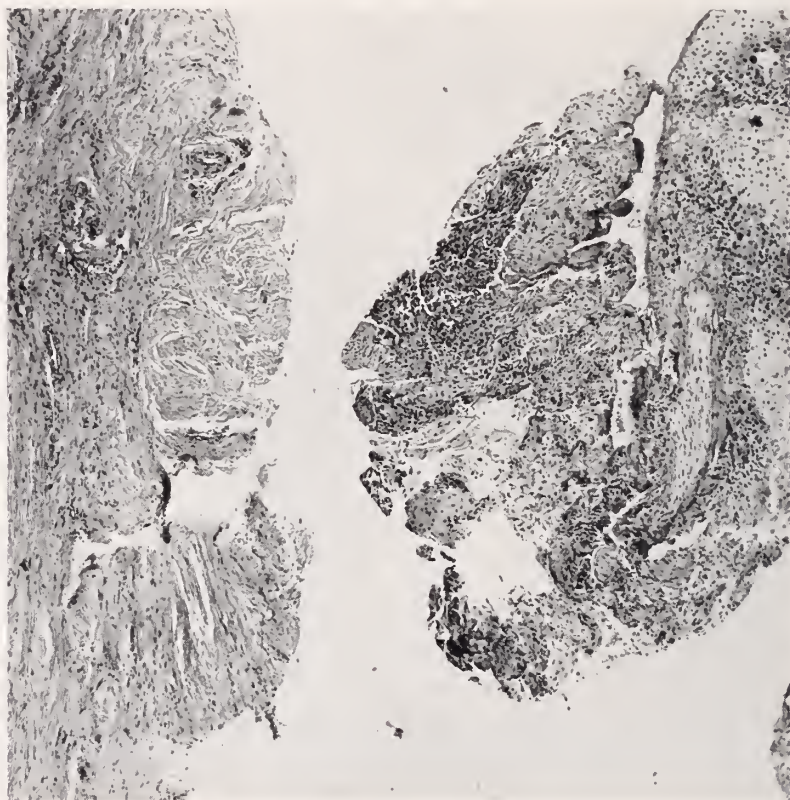


FIG. 1. *Case 1.* Photomicrograph of tissue removed from sheath of carotid artery

The excised area was fully  $1\frac{1}{2}$  inches in diameter and extended into the body of the muscle. It was immediately covered by a split thickness graft from the thigh. This has healed. The small ulcer over the carotid bifurcation slowly healed. It is now three years since the last operation, and there has been no further trouble, no further local recurrences in her neck. She lives a normal life and has regained her strength (fig. 3).

*Case 2. History.* Mr. L. M., aged 72 years, was first seen by me on October 22, 1946. He had a carcinoma in the posterior third of the left side of the tongue. It had been treated on January 31, 1945 with radon seeds (8.2 millicuries). Clinical regression was satisfactory. At the time of insertion of the seeds into the tongue, he had a node  $1\frac{1}{2}$  cm. in diameter in the left sub-maxillary area. He persistently refused operation, and it was only now, ten months later, when the node had grown to perhaps three or four times its previous size, that he consented.

*Examination.* The patient was a rather wiry Italian workman, showing signs of hyper-

tensive heart disease, an occasional cardiac extra systole, and slight cardiac enlargement. The lesion in the tongue seemed controlled. There was only a healed scar palpable in the left posterior portion of the tongue. Behind and below the angle of the mandible there was a mass 3 centimeters in diameter in the subdigastric region. One or two smaller nodes could be palpated anterior to this.

*Course.* It was not certain whether the risk of a radical neck dissection was justified,



FIG. 2. *Case 1.* Appearance in September 1947. Residual disease (x) at carotid bifurcation, also necrotic ulcer over trapezius muscle (y). Radon implantation at (x); wide local excision (y) were done.

but it was finally decided that such an attempt was worthwhile, particularly since it was beginning to be difficult to control his pain.

A left radical neck dissection was done on November 13, 1946. In the resection the lower neck and supraclavicular triangle were routinely dissected. The submental and submaxillary triangle were easily cleared. However, in the region of the posterior digastric muscle the tissues were quite firm and fibrous. This was getting close to the lymphatic drainage area of the posterior portion of the tongue where the original lesion had been. During the course of the dissection of this region, from the posterior digastric to the mastoid eminence,

it was not certain whether one was cutting through irradiated tissues or through a metastatic process. Convalescence was smooth and the patient left the hospital on the ninth day.

Five months later, in March of 1947, a recurrence was noted immediately posterior to the angle of the mandible, between this region and the mastoid eminence, and beneath the lower portion of the ear lobe. It was fairly movable and apparently distinctly local. It was not in the exact field of the original metastatic deposit, but immediately posterior



FIG. 3. *Case 1.* Appearance, April 1950, 3 years after last operation

to that site. Since he withstood the previous operation well, it was decided to try to remove the recurrent lesion high in the upper posterior region of the neck.

On March 29, 1947, a wide skin excision was made to circumscribe the mass. The lower portion of the parotid gland was dissected exposing the facial nerve in the interior of the parotid gland. The carcinomatous mass infiltrated the region below the parotid gland, and immediately internal to the angle of the jaw. The mass extended toward the floor of the mouth, in the neighborhood of the original lesion and backward to the lateral pharyngeal



wall. The hypoglossal nerve apparently passed directly through the carcinomatous mass, and had to be sacrificed.

The post-operative course was uneventful, and five days later the open area was covered with a skin graft about 2 inches in diameter.

However, he was left with paralysis of the left side of the tongue and the left vocal cord was fixed. Apparently, the vagus had been very close to the mass and was injured. He could nevertheless eat well and was active enough to look after his affairs and do some light work.

In August of 1947, an area of granulation was noticed behind the angle of the mandible. It became larger, and in October 1947 there was another recurrent area immediately posterior which in time became ulcerated. These areas were treated by repeated cauterization; they healed partially, leaving an area of persistent recurrence immediately in front of the



FIG. 4. Case 2. Male aged 73. Appearance on May 15, 1950. Radical neck dissection was done 11-13-46. Primary in left side of posterior tongue had been controlled with radon implants. Local recurrence behind angle of mandible dissected out 3-29-47. Further recurrence in front of mastoid treated by irradiation (X-ray plus radon implants) February 1948. Well two years.

mastoid eminence. It was behind the ear—posterior to the location of the first recurrence, in the region of the posterior portion of the parotid gland. Well localized roentgen ray therapy was thought desirable, and in February 1948 he was given 3,600 roentgens in air to each of two lateral ports, aimed directly at the center of the left and right mandibles, with cross-firing at the base of the tongue. (The site of the primary lesion was the posterior portion of the left side of the tongue.)

Mucositis was produced along the posterior portion of the base of the tongue, along the ulcer crater of the recurrent carcinoma in the skin of the neck, and along the left side of the angle of the mouth. There was a satisfactory regression. On April 12, 1948, 7 millicuries of gold radon seeds were placed in the base of the tongue through the midline of the neck.

The local recurrent areas have healed. He, at present, has remained well for two years, since his last treatment. He eats soft foods fairly well and can get about and do light jobs, and is free of pain (fig. 4).



## SUMMARY

Two cases of primary malignancy of the tongue are described. In both instances there were metastases in the neck which were treated with persistence by surgery and irradiation with results quite satisfactory as to survival period and rehabilitation.

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# INTESTINAL OBSTRUCTION COMPLICATED BY PREGNANCY

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Intestinal obstruction in itself is a serious disease and is accompanied by a high mortality and morbidity. When complicated by pregnancy intestinal obstruction poses difficult additional problems in diagnosis and treatment. The incidence of intestinal obstruction in pregnancy is fortunately small. Williams (1) at Johns Hopkins noted an incidence of 2 cases in 30,000 pregnancies; Weintraube and Joffe (2), 3 in 32,000 (3); Barone et al, 6 in 45,000; Smith and Bartlett (4), 1 in 66,430; Bemis (5), 2 in 15,000; Siegel and Pleshette (6), 1 in 4,445. Bloch and Sales (7) were able to collect only 22 cases of intestinal obstruction from 33 hospitals in Philadelphia over a 10 year period. The actual incidence is probably somewhat higher than reported by obstetrical services since no doubt some patients are operated on on surgical services and are not reported.

The case report which follows is unusual insofar as this patient had acute small bowel obstruction in the third and fifth months of two successive pregnancies. Exploratory laparotomy was done in each instance and the patient delivered per vaginam of normal infants.

## CASE REPORT

This patient, a 32 year old primigravida, with a normal menstrual history, was first seen on May 5, 1946. Her last menstrual period had occurred on February 8, 1946. The chief complaints were generalized abdominal pain and distention of 14 hours duration. Bowel movements were normal and the last one had occurred on May 5, 1946. There had been no vomiting. The significant past history included an exploratory laparotomy for intestinal obstruction 10 days following an appendectomy in 1941. There had been no gastrointestinal symptoms in the interval. A subtotal thyroidectomy for an adenoma of the thyroid was done in 1942.

*Examination.* The patient was a thin, asthenic, acutely ill woman. Her blood pressure was 100 systolic over 70 diastolic; temperature, 98°F; respirations, 20 per minute. The abdomen was markedly distended and tympanitic; and an obvious ladder pattern of the small bowel was visible through the thin abdominal wall. On auscultation the abdomen was silent for the most part with infrequent sibilant sounds. The uterus was enlarged to the size of a 10 weeks' pregnancy and the adnexa were not felt. The laboratory findings were as follows: Urine, normal; hemoglobin, 11.5 Gm., red blood cells, 4,460,000; white blood count, 12,500 with polymorphonuclears, 79% (66% segmented forms), small lymphocytes, 20%, and monocytes, 1%. Roentgen examination of the abdomen in the erect position revealed small bowel distention with fluid levels. A Miller-Abbott tube was inserted, intramuscular penicillin therapy begun and alternating solutions of 5% glucose in distilled water and physiological saline were administered intravenously.

*Course.* On May 6, 1946, 9 and 15 hours after the previous film, X-ray films showed the Miller-Abbott tube well down in the small bowel and decreasing intestinal distention. The following morning the condition of the patient declined: the temperature was 100°F, and the abdomen was distended and tender. It was felt that continuation of decompression therapy was dangerous and the abdomen was explored by Dr. E. Jemerin, the consulting surgeon.

The small bowel was found to be moderately distended throughout. The obstruction

was due to a volvulus of the proximal ileum and secondary kinking of the small bowel by adhesions. Numerous adhesions, binding together various segments of ileum and fixing a few tightly to the bladder and fundus of the uterus, were encountered. These adhesions produced kinks in the small bowel and were secondarily responsible for the superimposed intestinal obstruction, once the bowel had become distended by the primary focus. The primary focus proved to be a complex volvulus in the proximal ileum. The bowel at this point was tied into a slip knot and fixed there by the developing distention. There was minimal impairment of the circulation at this point. The Miller-Abbott tube was felt just proximal to the site of obstruction. On entering the abdomen the numerous adhesions of bowel to the parietal peritoneum were divided. The ileocecal junction was identified and the bowel delivered progressively from this point. The adhesions were separated as encountered. As each of these were separated, some relief of the local kinking was obtained. Finally the primary lesion was reached and the slip knot readily reduced. The obstruction seemed completely relieved when this was accomplished.

The postoperative temperature varied between 100° and 102°F for 4 days and then remained normal. For a few days the distention appeared to increase then gradually subsided. The Miller-Abbott tube was continued for 5 days. Intravenous fluids and penicillin were administered during the same period of time. The abdominal wound healed by primary union and the patient was discharged on the 16th postoperative day.

The patient went into spontaneous labor on November 15, 1946, approximately 6 months after the operation. After a long, arduous labor of 48 hours, she was delivered by prophylactic low forceps, following a median episiotomy, of a 7 pound 14 ounce normal male infant. The postpartum course was afebrile and uneventful.

The patient remained well until March 8, 1948 when she had a spontaneous incomplete abortion of 6 weeks duration. The uterus at this time was evacuated of several necrotic fragments of placental tissue.

The following year she again became pregnant. Her last menstrual period occurred on May 16, 1949. There were no gastrointestinal symptoms until October 19, 1949 when she was approximately 5 months gravid. Following dinner there was sudden onset of sharp, paroxysmal epigastric pain. One hour later there was vomiting. She was immediately brought to the hospital. Abdominal examination revealed a soft, moderately distended, tympanitic, slightly tender abdomen. A soft uterus was palpable 3 finger breadths above the symphysis. The white blood count was 20,900; red blood count, 3,360,000; and hemoglobin, 10.5 Gm. X-ray examination of the abdomen in the erect position revealed slight dilatation of the small bowel with traces of gas in the colon. Few fluid levels were present but according to the roentgenologist the picture was "not pathognomic of mechanical obstruction." His diagnosis was ileus with slight distention of proximal bowel.

Intravenous fluids and Miller-Abbott tube were started. The abdominal distention and tenderness increased. Subsequent X-rays revealed the Miller-Abbott tube in the duodenum with small bowel distention unchanged. The abdominal cavity was explored 36 hours after the onset of symptoms. A small amount of serosanguinous fluid was present. In the left side of the lower abdomen a firm adhesive band adherent to uterus and small bowel was binding down a segment of bowel approximately 15 to 20 inches long. The closed loop had twisted upon itself  $1\frac{1}{2}$  times and had formed a slip knot which further imprisoned a shorter segment of involved intestine. The bowel was purplish in color and covered with a plastic exudate but viable. The band was divided and the bowel untwisted. The abdominal wall was closed with figure of eight wire sutures through fascia and peritoneum. Postoperatively the distention increased and the temperature ranged between 100° and 101°F. On the fifth day postoperatively there was a sudden marked decrease in distention following an enema. The patient was discharged 12 days postoperatively.

She remained well until the spontaneous onset of labor on Feb. 20, 1950 and delivered spontaneously of a normal 7 pound 12 ounce infant after a short labor of 5 hours.

# DISCUSSION

Reliable mortality figures, fetal or maternal, in intestinal obstruction complicated by pregnancy are difficult to obtain since the experience of any single individual or hospital service is small. Reference to Table I indicates the maternal mortality as reported by 3 authors. These results were obtained by the compilation of individual cases reported in the literature, during the periods indicated.

Hanson (11) in 1941 from a review of the English literature concluded that the maternal mortality was approximately 25% and the fetal mortality was 36%.

It is interesting to compare the mortality in intestinal obstruction complicated by pregnancy with ileus in general. Smith and VanBeuren (12) from the Presbyterian Hospital reported a mortality drop from 66% (1916-1919) to 24% (1935-1939) in acute ileus. It will be noted that these figures are not significantly different from those in ileus complicated by pregnancy. Smith and VanBeuren attributed their improved results in part to the use of the Miller-Abbott tube in

TABLE I

AUTHOR	YEARS	CASES	AVERAGE MORTALITY
Ludwig (8).....	1913	95	54%
Mikulicz and Radeki (9).....	1913-1925	80	39%
Eliason and Erb (10).....	1925-1936	66	21%

1938 and 1939. However the improved results noted in Table I antedated the Miller-Abbott tube which was introduced in 1937. The increased knowledge of electrolyte and fluid requirements, the advent of antibiotics, and increased use of blood transfusions have no doubt contributed to the decreased mortality.

*Etiology.* Postoperative adhesions and bands leading to mechanical obstruction are the etiological factors in more than 60% of the reported cases. Inguinal and femoral hernias produce ileus in less than 5% of the cases. This low incidence is due to the fact that the small bowel is displaced out of the pelvis by the enlarging uterus which effectively blocks off the hernial openings. The most frequent site of obstruction is in the terminal ileum. Tumors, cysts, foreign bodies and pregnancy per se are other etiological factors reported.

The German literature contains several references to ileus associated with pregnancy in the absence of any other ascribable cause. This subject has received little attention in the American literature and normal pregnancy as an etiological factor in the production of ileus, is questioned by many.

An excellent review of the subject presented by Eliasson and Erb (10) leaves little doubt that the growing uterus can produce obstruction by compression of the sigmoid against the bony pelvis. Other factors, in addition to pregnancy, would appear to be necessary for the production of obstruction, such as increased



constipation, postoperative paresis, redundant mesocolon, and autonomic system disturbances.

The obstruction is always in the region of the rectosigmoid colon and a barium enema is helpful in the differential diagnosis. Several instances have been reported of successful treatment by knee-chest position and the passage of rectal tubes past the site of obstruction. In other cases the condition was cured only by evacuation of the uterus and resection of the redundant colon.

According to Hansen (11) in an analysis of 80 cases of intestinal obstruction in pregnancy more than 55% occurred during the third trimester with approximately 10% occurring postpartum or during labor. However a significant number of cases have been reported during each month of pregnancy.

*Differential Diagnosis.* The differential diagnosis may be difficult since all of the cardinal symptoms of obstruction, vomiting, colic, obstipation, and distention, may appear in normal pregnancy. Obstruction should be suspected if any of the above symptoms occur in a pregnant woman with a postoperative abdominal scar. The nausea and vomiting of pregnancy is usually accompanied by a flat, non-tender abdomen; distention and tenderness are uncommon. X-ray of the abdomen in the erect position is usually diagnostic in doubtful cases, but may be negative. It should be emphasized that not infrequently gas and stool may be passed in the presence of a high small bowel obstruction.

*Management.* In the presence of mechanical obstruction, to delay surgery in favor of observation with intestinal intubation is dangerous and is probably only permissible for a short while in order to relieve distention and get the patient into satisfactory fluid and electrolyte balance. If the diagnosis were made early enough and surgery resorted to the maternal mortality could be reduced to below 1%. To wait for signs of strangulation, increasing distention, and electrolyte changes as indications for surgery invites a high mortality. The latter doubles when resection is necessary. The obstruction should be treated surgically with complete disregard for the pregnancy.

The value of hormone therapy to prevent onset of labor is questionable. Progesterone, 30 milligrams daily in divided doses and/or combined with di-ethyl stilbesterol 100 milligrams daily have been advocated.

Prior to viability of the fetus, it is generally agreed that the uterus should not be disturbed. When dealing with a full-term uterus, some authors have advocated routine emptying of the uterus to avoid the onset of labor and subsequent strain on the abdominal wound. We believe that the routine Cesarean section would merely increase the morbidity and mortality.

If the uterus, however, does not permit adequate exposure it must be emptied or even removed, contrari-wise if exposure is adequate the uterus should not be disturbed. Abdominal closure with silver wire should be sufficient to prevent wound dehiscence if labor intervenes. A number of patients have gone into labor immediately postoperatively, and the abdominal wall has remained intact. However, evisceration has been reported, usually in association with infection.

A lowering of the high mortality in intestinal obstruction complicated by

pregnancy may be anticipated, if the following precepts are kept in mind; early diagnosis and surgical intervention; adequate pre- and postoperative decompression by intestinal intubation; accurate maintenance of fluid and electrolyte balance; administration of sulfonamides and antibiotics as indicated; and the liberal use of blood transfusions.

# SUMMARY

A case of acute intestinal obstruction during the third and fifth months of 2 successive pregnancies is described.

A brief review of the literature and discussion of the diagnosis and treatment are presented.

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## CALCULOSIS OF THE URINARY TRACT IN EGYPT

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Calculi of the urinary tract are in Egypt, like in the rest of the world, the main concern of the urologist. Most of the causes observed elsewhere are also found in this country; but there are many other factors, hardly known abroad, which are contributing here on a large scale to the urinary lithiasis. A great deal of items have been cited as being responsible for calculus formation, but in most cases the etiology is based on the concurrence of different pathological processes or physiopathological deviations.

Normally, the materials that will constitute the calculi are dissolved in the urine. In case the equilibrium, liquid—crystalloids, is disturbed, precipitation of the latter will occur and a favorable basis for calculus formation is thus created. This factor, however, is not playing the only or even a predominant role; many patients showing phosphaturia, oxaluria, etc., do not manifest calculi formation during their whole life. An important factor favoring the precipitation and accumulations of crystalloids is a disturbance in the normal urinary excretion. A stricture or stenosis or even perhaps nervous disorders in any part of the urinary tract may lead to calculus formation. Infection and mainly chronic infection have a paramount influence and a large variety of bacterial agents has been found in patients suffering from urolithiasis.

Glancing at the geographical distribution of the urinary calculi, it will be found that in "calculi areas", e.g. in Central Russia, urolithiasis is wide spread, whereas in Ireland, it is a rare occurrence. Its high frequency in *Occidental* Asia is contrasted with its rareness in *Oriental* Asia. Geological, climatic, racial and constitutional circumstances are in this connection significant.

The influence of highly mineralized water emphasized by certain authors (Abderhalden, Hanslyan, etc.) is denied by others (e.g. Lichtwitz) who are pointing out that in the province of Hesse (Germany) calculi are rarely seen in spite of the strongly calcareous water.

Diet plays certainly an important role in calculi formation. Exclusively pap-nourished infants are subject to urolithiasis on a rather astonishing scale. In Dalmatia where the infants are living on wine, liquors, smoked meats, etc. calculi are encountered even in infants at the age of two months. In Egypt we often have occasions of operating on one or two year old infants for urinary calculi, especially of the bladder. Here, too, the influence of inadequate feeding is notorious. Various authors are incriminating metabolic changes, glandular disturbances or Vitamin A deficiency. In my opinion the antagonism between Vitamins D and A has to be borne in mind in Egypt with regard to a potential extensive sun exposure and its consecutive Vitamin D production.

Elvejani and New advance the theory that Vitamin A deficiency produces dysfunction of the renal epithelium and consequently pathological precipita-

tion of the normally diluted salts. The interesting experiments of Ch. C. Higgins proved the possibility of stone production in animals—similar to those of patients—by feeding the animal on a diet deficient in Vitamin A.

I shall not insist on items well known in other countries and limit myself to the most important factor of urolithiasis in Egypt: The schistosomiasis or bilharziasis. Its important bearing on the pathology of the urinary tract becomes fairly evident if one considers that over 70% of the Egyptian population, especially the peasants, have been affected once or on several occasions by this disease. Bilharziasis was already known in Ancient Egypt. Bilharzial ova were found microscopically in the urinary tract of mummies; at that period the pathogeny was already known although the way of contamination was a guess.



FIG. 1. Photograph of kidney stones found in skeletons of the First Dynasty Tombs (3200 B.C.).

It is a quite interesting fact to note that the Ancient Egyptians considered the Nile water as the source of this disease. Some of them attributed its sometimes reddish color to the admixture of bloody urine and alleged the extraordinary fertility of the Nile Valley as its consequence.

Through the kindness of Mr. Zaki Y. Saad, Director of the Royal Excavations at Helouan, I am privileged to include a photograph of kidney stones (fig. 1) found in skeletons of the First Dynasty Tombs dating back to about 3200 B.C.

The pathogenesis as well as the symptomatology of nephrolithiasis are much alike in Egypt as well as elsewhere all over the world. It differs however, with respect to the rest of the urinary tract. It is understood that in this category do not enter calculi originating in the kidney but only stopped during their migration in the ureter. Abroad primitive calculi are very rarely encountered.

In order to avoid misunderstanding we may term them also autochthonous



stones, i.e. calculi formed *in loco*. They are sometimes seen after an ureterolithotomy with sutures. In this case a stitch may become the starting point for calculus crystallization. I have published such an incidence in 1929.

In the urological literature there are recorded cases of periureteritis following an adnexitis (male or female) with subsequent calculus formation. But it is a matter of fact that these cases present a small percentage compared to the tremendous number of primitive calculi due to pathological effects of schistosomiasis. The anatomical changes of the ureter affected by bilharzia are very important. The ova of *Schistosomum haematobium* reach the ureter through the



FIG. 2. Plain X-ray. Pronounced calcification in and around the bilharzia ova produces—on a variable scale—radio-opacity. Bladder and ureters are discernible roentgenologically.

venous system at different levels and especially at its lower third. A defense reaction develops with an appeal to lymphocytes and eosinophiles—sometimes giant cells. Then fibroblasts are carrying out a surrounding action.

A nodule is formed resembling very much a tuberculous nodule. This unit may be called a “bilharzioma”. Once the ova reach the submucosa, pathological changes of the epithelium-lining are taking place. In the beginning the mucosa becomes rough and irregular, covered by “sandy patches”. At a more advanced stage granulomatous or papillomata-like formations are constituted. The ova provoke a degeneration of the submucosa and impair the muscle contractibility.

The next stage is represented by stenosis or sclerotic stricture of the ureter, sometimes with different degrees of calcification. Taking into account the epi-

thelial desquamation, one may easily understand how the precipitation of the urinary crystalloids are enhanced by these pathological conditions resulting from

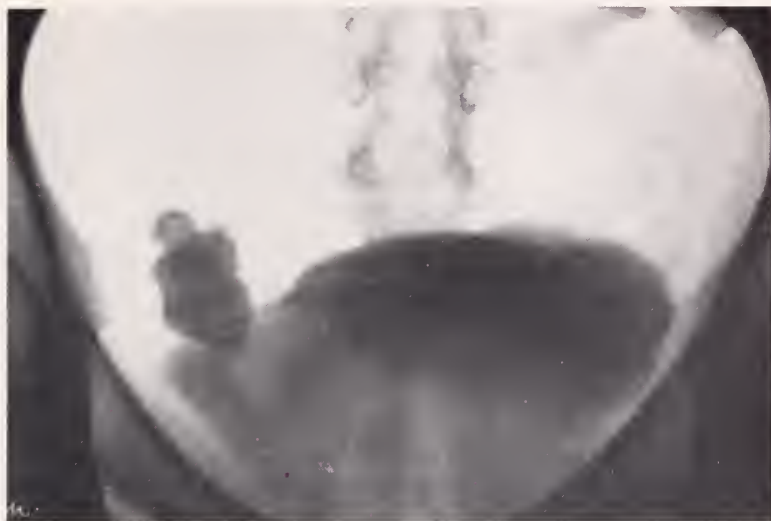


FIG. 3. Plain X-ray, showing irregular non-homogenous juxtavesical calculus of the right ureter. Excretory urographic examination revealed opposite to this calculus shadow a crescent-shaped filling defect corresponding to a bilharzial tumor at the ureteric orifice. The cystoscopic biopsy and histological examination proved the cystic nature of the new growth containing numerous calcified bilharzial ova.

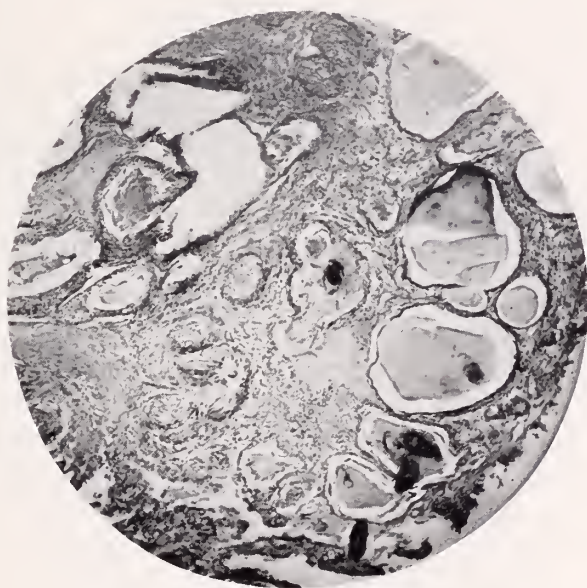


FIG. 3a. Photomicrograph showing cystic bilharzial tumor containing calcified bilharzial ova.

the just mentioned physiopathological damage of the ureter thus creating a basis for calculus formation.

The calcification gives radiologically a picture characteristic of bilharzial changes (fig. 2).

The other bilharzia manifestations of the ureter may be revealed by instrumental or excretion urography. We are using sometimes a combined contrast medium, air urography, in order to detect papillomata or stones with poor x-ray opacity.



FIG. 4. Multiple calculi of the lower end of the left ureter. Stricture above calculi. Small juxtavesical stone of the right ureter.

An interesting case of stone and simultaneous papilloma formation around an ureteric orifice is seen in Fig. 3 and Fig. 3a (photomicrograph).

More frequently than it is generally supposed ureteral calcuolosis is associated with bilharzia. When scouting urolithiasis one discovers the calcifications and deformations of the ureter (fig. 2). The ureteral calculi in their migration from the kidney are definitely arrested by the bilharzial stricture. These calculi progress in size by precipitation of the salts contained in the urine (clearly seen in

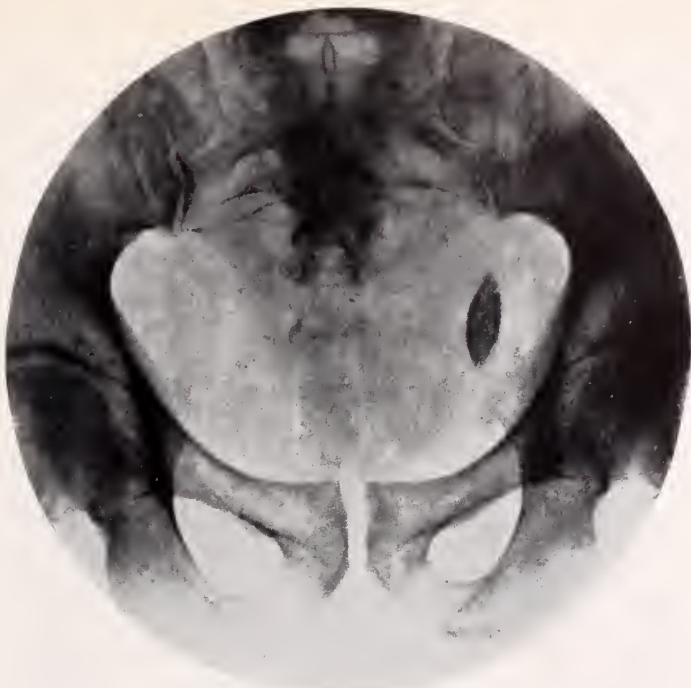


FIG. 5. X-ray film, showing calculus of ureter.

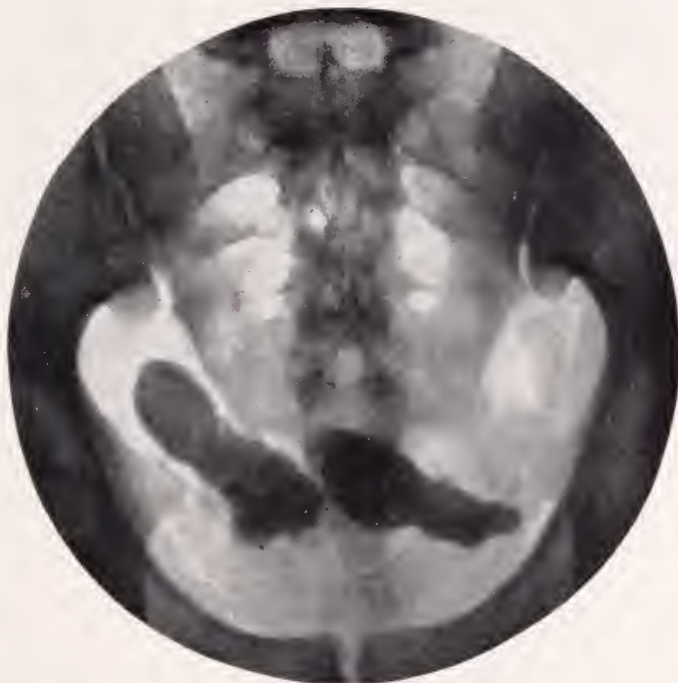


FIG. 6. Plain X-ray. Enormous bilateral stones of ureter. Clinically, mild urinary trouble.



fig. 3). We, on the other hand, admit the formation of ureteral calculi "*in loco*".

This autochthone lithogenesis is facilitated in bilharzia by the stagnation of the urine in aneurysm-like pockets above strictures (fig. 4) and by the presence in the urine of foreign bodies (ova); the latter are prone to form the nucleus of the calculus. No doubt that the eventual concomittant infection constitutes a favoring factor.

The radiological findings support the assumption of potential primitive calculus formation by the following items;



FIG. 7. Plain X-ray. Numerous stones of the left ureter. Calculus of the right pelvic ureter. No nephrolithiasis, no clinical symptoms.

- 1) pronounced ureteral calculosis without any previous sign of nephrolithiasis; sometimes spindle-like shape is somewhat characteristic. (fig. 5).
- 2) frequency of multiple and large sized bilateral ureteral calculi. (figs. 6, 7).
- 3) Calculi superimposed between multiple strictures where a crossing is impossible. (fig. 8).
- 4) absence of symptoms in the beginning and sometimes over a long period of autochthone calculus formation as compared with the pronounced colicky pain of the migrating one.
- 5) the particular shape of calculus casting often pathologically changed ureter (kinks, strictures, dilatations.) (figs. 9, 10).

Giant stone formation of the urinary tract are in Egypt met with in adoles-

cents and young people. One is astonished sometimes to discover them occasionally during a routine examination, the patient showing merely slight symptoms. A flat x-ray showed a bilateral enormous nephrolithiasis. A 25-year old Egyptian peasant, suffering from bilharzia for many years. He had minimal general and urinary symptoms and exhibited no change in his condition



FIG. 8. Plain X-ray. Two primitive superposed calculi in each ureter above bilharzial strictures. Each ureter presenting two big calculus shadows in a certain distance from each other. These stones have their origin above bilharzial ureteral strictures, probably formed "in loco". No history of renal colics; no calculi in the kidney.

during observation for several years. In another patient, aged 23 years, a plain x-ray disclosed giant bilateral calculosis in a horseshoe kidney (fig. 12).

*Figure 13* is that of an excretory urography. Here is seen an enormous bladder stone nearly filling out the whole pelvis with only little changes in the upper urinary tract. Different concentric layers of the stone are seen. The weight of the extracted stone was 400 grams. The patient complained only of some frequency and incontinence.

*Figure 14* is a plain x-ray, showing an enormous calculus in the prostatic urethra of a 23-year old Egyptian, affected by long standing bilharzia. The stone was removed by perineal route.

If the preceding conditions are borne in mind, one may realize that we are entitled to speak of a genuine "Egyptian (Bilharzial) Urology". The urological



FIG. 9. Plain X-ray. Giant calculus casting a highly dilated and tortuous left ureter.

surgeon will be confronted with different problems of surgical treatment and postoperative management. The irreversible damage to the urinary system will explain the high incidence of recurrent calculus formation.

The anatomy of the ureter is often completely changed and difficult physiopathological problems will sometimes emerge. The troubles of the urologist will start now and then after the removal of the calculus. Further, one has to be conservative owing the often bilateral condition and to the sometimes still per-



FIG. 10. Plain X-ray. a) Bladder stone of hen's egg size and shape. b) Hazelnut sized stone of right pelvic ureter. c) Large ureteral stone on the left lower end. The shadow has somewhat a spermatozoid-like appearance. The strange shape is probably produced by autochthone formation.



FIG. 11. X-ray film showing enormous nephrolithiasis.





FIG. 12. X-ray film showing giant bilateral calculosis in a horseshoe kidney.



FIG. 13. Excretory urography showing enormous bladder stone



FIG. 14. Plain X-ray film showing calculus in the prostatic urethra.



FIG. 15. Instrumental urography. Filiform stricture of ureter. Patient, 25 years old, suffering from severe right renal colics. Ureteric catheter stops after 5 centimeters. Anyhow the opaque liquid passes through and demonstrates a filiform stricture. Successful transversal resection was performed.

sistent action of the primary agent. During an operation great difficulty is experienced in extracting even larger calculi in a tortuous and intestine-wide ureter. In such ticklish cases, the inexperienced surgeon may be caught by the stone and not vice-versa.

A guiding ureter-catheter will not be felt and strictured ureteric orifices make even its introduction often impossible. Bilateral ureteric stones are better dealt with by mid-line incision and extraperitonization of the bladder lest to be trapped by extensive adhesion to the peritoneum or enormously dilated venous plexus. It is astounding how quick large wounds are healing in the lower end of the ureter, probably due to its high vascularity.



FIG. 16. Intravenous urography. Stricture of the juxtavesical portion of the ureter: adhesive periureteritis. Operative control. Reimplantation of the ureter in the bladder.

Transversal resections of the ureter may be successfully performed (fig. 15) and a stone above an impassible stricture at the lowest part of the ureter indicates a reimplantation in the bladder (fig. 16), provided the latter is not too badly damaged. Needless to say how difficult it may be to decide as to the possibility of reimplanting a calcified or fairly enlarged ureter. Experience is here as always the best teacher, but nevertheless depressing drawbacks are discouraging. Occasionally a surgeon and a patient may become fellow-sufferers and at the end the radical nephroureterectomy—if possible—remains the only solution.

#### COMMENT

We may conclude that the surgery on the upper urinary tract, severely damaged by bilharzia, remains a complicated surgical problem and the operation at

the best a difficult one. The leitmotif in surgery of bilharzia should be, still more than in usual urinary tract operation, as conservative as possible and radical as necessary.

The postoperative management in Egypt is fraught with various difficulties. It should be well understood that principles of postoperative management do not differ here from those generally practised: elimination of stasis as well as focus of infection; eradication of infections in the urinary tract; correction of metabolic diseases; administration of large amounts of Vitamin A for a long period, and, last but not least, the dietary management. The latter problem is a crucial one because the poor class is living on fare which is deficient in certain essentials.

The principal concern remains the arrest of the bilharziasis itself. Notable progress has been achieved as well with respect to prophylaxis and to treatment. The chemistry blessing the mankind by numerous wonder drugs will not fail to find also a radical panacea for bilharziasis—let us hope in the near future.

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## RENAL PTOSIS\*

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There has been no more debatable subject than renal ptosis, at least as to its treatment. Many and varied symptoms have been ascribed to a freely movable kidney and many and various operative procedures have been devised to replace and fix high in its fossa the so-called ptotic kidney. The fact that so many operations were done for this condition without relief of the patient's symptoms prompted urologists to completely review and re-evaluate their experiences. Some, however, still consider surgery indicated in every case of demonstrable renal ptosis.

Birdsall of Philadelphia is one of the most ardent advocates of surgery for every freely movable kidney. There is, however, a growing tendency upon the part of urologists to take a middle position in the treatment of these cases. We belong to that group which feels that only those movable kidneys in which the symptoms are positively proven to be caused by the abnormal mobility of the organ should be considered for surgical treatment. These cases must, in our opinion, be very carefully studied and the operative cases meticulously selected.

We have demonstrated repeatedly that mobility of the kidney alone is no indication for surgical therapy (figs. 1, 2, 3, 4 and 5). Bilateral ptosis is usually accompanied by general visceroptosis. In these cases surgery to correct the renal ptosis alone is usually contraindicated (figs. 6 and 7). The excursion of the kidney in deep inspiration and expiration and in changing from the supine to the erect position may be as much as 12 cm. without producing symptoms. The kidney with less than a 12 cm. excursion may be easily palpable, especially in a thin individual, without producing symptoms or evidence of renal pelvic damage, and no treatment is indicated. Another kidney may have very little excursion and yet may produce both symptoms and evidence of renal pelvic damage and may be considered for surgical treatment.

Every year we see many patients who are referred to the clinic with requests for nephropexy, who are discharged without surgery because we are unable to satisfy ourselves that surgery will relieve them of their complaints and because we cannot demonstrate, to our satisfaction at least, that there is any reno-pelvic disturbance.

The position of a kidney is not too important. For example, a pelvic kidney usually functions well without symptoms and usually needs no surgical treatment unless a pathological process develops which would require surgical therapy in a normally situated organ, or if its position may obstruct the pelvic outlet in labor. Then it must be demonstrated, as in the normally situated pathological kidney, that a normal contralateral kidney is present. All of these pelvic kidneys,

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as a rule, are palpable, and many have been operated upon, particularly in women, because they were diagnosed as pelvic tumors. We usually consider a movable or ptotic kidney to be one that disappears in the renal fossa under the costal cage with the patient in the supine position, yet one that can be palpated and held down manually when the patient takes a deep breath or, in the erect position, the organ may be manually replaced high under the costal cage. These kidneys may or may not have normal excursions and they may or may not be tender to palpation. The condition may also be bilateral. The proportion of females to males suffering from ptosis is about ten to one.



FIG. 1



FIG. 2

FIG. 1. G. T., female, age 50. File No. 494343. C.C.: Pain in lower back. X-ray: Lower pole of right kidney below iliac crest. No Operation. No symptoms referable to kidney.

FIG. 2. M. McK., female, age 66. File No. 493230. C.C.: Backache and frequency of urination. X-ray Diagnosis: Ptosis, right hydronephrosis. No operation. No symptoms referable to kidney. Relieved by belt. (N. B. X-ray photographed in reverse).

We have come to the conclusion that it is very difficult to evaluate the symptoms due entirely to renal ptosis. Our experience in the clinic over many years conforms with that of many other observers, that renal ptosis without definite subjective symptoms and evidence of renal pelvic damage is not an operable condition. We believe that the subjective symptoms of real importance are postural backaches, with or without definite gastrointestinal disturbances.

Backache must be very definitely defined. Ordinarily, the pain is not constant but develops after the patient has been on her feet for several hours and usually becomes continuously worse the longer the patient is up and around. The distress usually is partially or completely relieved when the patient lies down, with or

without elevation of the hips. The pain is constantly in the same place and the patient generally can actually place her hand on the spot that hurts. There may or may not be acute attacks of Dietl's crises.

There may be definite gastrointestinal symptoms, particularly nausea, although many cases do not conform. Vomiting is not the rule, although with an acute attack of Dietl's crises this may be a very annoying symptom. In a limited



FIG. 3

FIG. 3. L. V., female, age 37. File No. 494621. C.C.: Pain in suprapubic area. X-ray: Right kidney falls 4 cm. Right Double Pelvis. No Operation: No symptoms referable to the kidney.



FIG. 4

FIG. 4. L. F. B., male, age 32. File No. 493416. C.C.: Backache, chills and fever. X-ray: Supine position. Ptosis, right kidney. Left also 5.5 cm. No Operation: No symptoms referable to the kidney. This patient has been treated successfully with a belt for  $1\frac{1}{2}$  years.

number of cases nausea may be the only symptom. Patients with recurring attacks of Dietl's crises may prefer surgery to any other type of treatment.

These same symptoms may also be caused by stricture at the ureteropelvic junction, kinks in the ureter, ureteral spasm, and other incomplete or complete obstructive lesions in the collecting apparatus. Given, then, a patient with an afebrile story of pain in the back, coming on after rising and getting worse toward evening, particularly after being on her feet all day, and being relieved by lying down, with or without raising the hips, with or without a palpable kidney in the erect posture, and with or without nausea, a non-infected, symptom-producing ptotic kidney may be suspected.

## EXAMINATION

The first procedure to assist us in confirming our suspicion (unless the patient has been sent to us with the definite diagnosis of ptosis which we always recheck ourselves) is an intravenous urogram with an erect urogram as soon as a good bilateral pyelogram can be obtained. This procedure will indicate whether or not retrograde pyelograms are necessary. Certain findings in the intravenous urogram may rule out the necessity for further cystoscopic and radiographic examinations. For example, if the pyelo- and ureterograms are perfectly normal in the supine



FIG. 5



FIG. 6

FIG. 5. L. F. B., male, age 32. File No. 493416. C.C.: Backache, chills and fever. X-ray: Erect position. Ptosis, right kidney. Left also 5.5 cm.

FIG. 6. F. D., female, age 56. File No. 162208. C.C.: Pain in the back. X-ray: Supine position. Bilateral ptosis, right hydronephrosis, general visceroptosis.

and erect positions, with no evidence of unilateral or bilateral trapping and no pyelectasis or calyectasis, there is little use to pursue the examination further. If the urograms are incomplete or show other evidences of renal damage, then further investigation is in order. During the past few weeks we have seen a patient whose intravenous and retrograde study showed no demonstrable abnormalities, yet bimanual palpation of the kidney revealed it to be a hypersensitive organ. In a case like this the only advice that can be legitimately given is "We do not believe that you have nephroptosis and therefore believe that a surgical approach is contraindicated; however, if no other source of your discomfort can



be found and if your discomfort is such that you wish surgery of an exploratory nature done, we will do it but with the distinct understanding that we cannot promise you any result." Occasionally, one will completely free one of these tender kidneys, sympathectomize them, and do an ureterolysis with astounding results but the reverse is usually the case. This is not ptosis, however.

With retrograde studies we are interested in several findings. A pathological kidney does not usually give severe colicky pain on over-injection. The normal



FIG. 7. F. D., female, age 56. File No. 162208. C.C.: Pain in the back. X-ray: Erect without belt. Bilateral ptosis, right hydronephrosis, general visceroptosis. No Operation: No symptoms referable to the kidney. This patient has been treated successfully with a belt for 4 years.

kidney almost always does. We try never to over-inject but often cause a severe pelvic spasm with only 1 cc. of pyelographic medium. Usually this is not the same type of pain from which the patient complains. We begin to consider the patient as a probable subject for the surgical treatment of the ptosis, first, if there are evidences of pyelectasis or calyectasis; second, if overdistention causes the duplication of the patient's soreness or pain; and third, if in the erect posture an ureteropyelogram shows the kidney to be definitely ptosed, with a high fixation of the ureter to the parietal peritoneum without intrinsic constriction of the ureter and a 10 to 20 minute delayed picture demonstrates trapping in the

renal pelvis. We always test these people with a belt or with some form of postural therapy to further prove that the patient with a normal non-infected ptotic kidney, if held in its fossa, is relieved of the symptomatology of which she complains. With all of the facts then before us, with all of our tests made, we consider surgery for relief. At times these studies must be repeated on different occasions before one definitely makes the decision to operate. The patient should be told the truth that operation may not relieve him or her but to the best of the physician's judgment, with all of the diagnostic criteria satisfied, the



FIG. 8

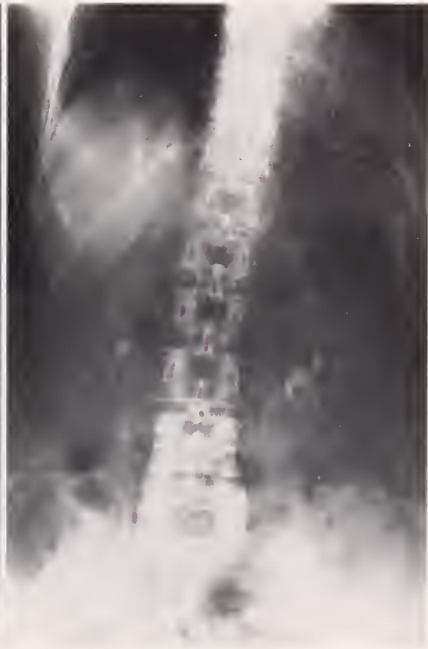


FIG. 9

FIG. 8. *Preoperative*. E. C. H., female, age 61. File No. 165469. C.C.: Dragging pain in right abdomen. X-ray Diagnosis: Bilateral ptosis, worse on right. Films taken in the erect position.

FIG. 9. *Postoperative*. E. C. H., female, age 61. File No. 165469. C.C.: Dragging pain in right abdomen. X-ray Diagnosis: Bilateral ptosis, worse on right. Films taken in the erect position. Operation: Right renal sympathectomy, ureterolysis and nephropexy. Subsequent X-rays: Right nephroptosis corrected.

chances for relief are very good. However, no more unhappy patient exists than one who expects complete relief after submitting to a major surgical operation if that relief is not forthcoming. Even with the exercise of the greatest possible diagnostic, preoperative and operative care a certain percentage of these people will not get the relief we hope to give them.

#### REOPERATIVE TREATMENT

The pre-surgical treatment, as practiced in our clinic, consists of bed rest for 48 hours, with the foot of the bed elevated at least 14 inches. The patient is allowed to raise her head only at mealtime. If this relieves or alleviates the

symptomatic ptotic kidney, then she is instructed as to the proper use of a ptosis or surgical belt which is to be worn at all times while up and about. In order to properly apply the garment, the patient must be in bed, preferably with the hips elevated and the belt fastened from the bottom up, pushing the abdominal contents before it.

Some individuals are completely satisfied with such an arrangement and wear the belt for years. Others become tired of the trouble of applying it and complain



FIG. 10



FIG. 11

FIG. 10. *Preoperative: Erect Position.* J. A. F., male, age 26. File No. 491763. C.C.: Painful urination, chills and fever. X-ray Diagnosis: Abnormally mobile right kidney with hydronephrosis.

FIG. 11. *Postoperative: Erect position.* J. A. F., male, age 26. File No. 491763. C.C.: Painful urination, chills and fever. X-ray Diagnosis: Abnormally mobile right kidney with hydronephrosis. Operation: Right ureteropelvioplasty, sympathectomy and nephropexy.

of the pressure it exerts on the abdomen. Nephropexy is advocated for these patients.

Some cases of symptomatic ptosis are not relieved by position and belt but may be by surgical replacement of the kidney in the renal fossa and so-called renal sympathectomy. It is to these individuals that no guarantee is given. Relief may be obtained but it is not positive. This should be clearly understood preoperatively.

#### OPERATIVE TREATMENT

It is our practice to do nephropexies without placing sutures through the renal parenchyma and we do not like to disturb the renal capsule. The 12th rib

is usually resected, the kidney is exposed and completely dissected free from all of the perirenal fat. The pedicle is also dissected free so that all of the vessels are completely isolated and the visible sympathetic nerve supply is destroyed. The pelvis and ureter are likewise dissected free and the ureter is stripped far down into the pelvis from its attachment to the posterior wall of the parietal peritoneum. All of the fine fascia-like bands around the pelvis, the ureteropelvic junction, and the ureter are also stripped off, and the kidney is placed high in its fossa under the dome of the diaphragm and it is watched for a few moments to see that there is no ureteral kinking. As a rule, but by no manner of means always, we hammock the kidney by suturing Gerota's fascia after the technique of Deming.

A pad is placed in the corresponding hypogastrium and pressure is brought to bear on the pad with dressing adhesive straps and the patient is returned to bed with the foot elevated 18 inches for 72 hours.

These patients usually suffer a great deal of pain for the first 48 hours. This is controlled with as little sedation as possible. The bed is placed in the normal position at the end of 72 hours, the pad in the hypogastrium is removed at the end of a week, and the patient allowed out of bed in 10 days to two weeks. The operative results are illustrated in Figures 8, 9, 10 and 11.

#### POSTOPERATIVE TREATMENT

Before leaving the hospital these patients are checked by a supine and upright intravenous urogram, for relief of symptoms, and told to take it easy for one month. They return for monthly rechecks for a period of three months, and if at the end of that time are symptomless, with pyelographic evidence of a kidney highly placed, a straight ureter and no trapping, they are discharged. They are then advised to return at once for a check-up if they have any return of their symptoms.

We see in our clinic a great many patients with kidneys that have been diagnosed as ptotic and symptom-causing. While we operate upon a fairly large number of these cases, the over-all percentage is very low, because we have found that unless the patient meets all of our criteria for surgery our results are not good. Years of experience have taught us that only good results will be obtained by nephropexy if ptosis is the cause of the patient's symptoms.

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## SUPRAPUBIC PROSTATECTOMY WITH HEMOSTASIS BY TRANSURETHRAL FULGURATION AND PRIMARY CLOSURE OF THE BLADDER

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Effective surgical management of obstructive uropathy caused by enlargement of the prostate calls for adequate removal of all adenomatous tissue in the benign cases, and removal of either the entire prostate or sufficient tissue in the malignant ones to provide a satisfactory vesical outlet.

Many surgical technics have been devised to achieve these purposes and the competent urologist must be proficient in all to enable him to apply the technic most suited for the individual problem. The intravesical suprapubic, the extravesical suprapubic, the transurethral, and the perineal routes all have been utilized with success, and no attempt will be made in this presentation to advocate the merits of one over the others in the treatment of benign prostatic enlargement. Most urological surgeons agree on the preference of a perineal approach for the removal of a carcinoma localized to the prostate gland, and on the use of transurethral surgery to relieve urinary obstruction in cases of prostatic carcinoma which either are locally inoperable or have metastasized.

It is believed by many urologists that the large prostatic hypertrophies may be removed most expeditiously by the suprapubic transvesical approach with the least morbidity hazard. Objections to this technic take form in (a) control of hemorrhage at the operating table and in the immediate post-operative period; (b) uncomfortable and messy dressings; (c) occasional persistent suprapubic urinary fistulae; (d) prolonged hospitalization.

Primary closure of the bladder following suprapubic removal of the prostate would minimize or totally eliminate the latter three objections providing the surgeon could secure adequate and dependable hemostasis at the time of operation.

Suture hemostasis of the bladder neck and prostatic fossa permitting primary bladder closure was proposed by Harris and Lower independently in 1927. Harris reported in 1936 a series of 371 cases in which this technic had been employed successfully with a mortality of 2.7%. However, the current opinion of the majority of urologists finds the technic difficult to perform in most individuals and prone to result in bladder neck contracture.

The absorbable hemostatic materials, Oxycel and Gelfoam, promised to be extremely useful in securing hemostasis following prostatectomy. However, fragmenting masses of these materials either plugged the drainage eyes of the catheters, or failed to dissolve completely. In some instances, scybalae of Oxycel provided a nidus for calculus formation. Despite these failings, Stump and Thumann in 1948 reported 15 cases, and Eikner 89 in which these substances had been used for hemostasis allowing primary bladder closure.

In 1948 David Davis suggested the use of a flexible electrode introduced through a panendoscope sheath as a method for controlling *delayed* hemorrhage

following any of the conventional types of prostatectomy. He accredited priority to Dr. Frank Hinman, Sr.

It has occurred to the authors that such a dependable and accurate method of hemostasis might be achieved by transurethral fulguration with the resectoscope, that a primary closure of the bladder might be carried out in cases of suprapubic transvesical prostatectomy.

Review of the literature reveals that McCarthy, in 1941, in a critique of the methods of prostatectomy then in vogue, suggested as a means for securing hemostasis following suprapubic enucleation of the gland, the transurethral introduction of the electrotome with subsequent coagulation of bleeding vessels. Although in his article he failed to state whether or not he had utilized the technic clinically, he mentioned by personal communication that he had used the technic several times with success.

The following is a report of our experiences with 63 cases in which such a method has been employed.

In addition to the usual array of instruments necessary for the performance of suprapubic prostatectomy, the armamentarium must include (a) an O'Connor rectal drape; (b) a resectoscope, preferably the Nesbit modification of the Stern-McCarthy instrument; (c) a #30 Fr. steel sound; (d) battery box with rheostat; (e) a surgical unit for cutting and coagulation.

In general a long acting spinal anesthetic such as Pontocaine has been preferred, although in hypertensives it is advisable to substitute intravenous sodium pentothal and curare to avoid marked drops in blood pressure, which might delude the surgeon as to the excellence of his hemostasis.

The transurethral use of the resectoscope requires the patient to be in a lithotomy position, with the legs supported widely abducted. The latter enables the surgeon to swing his head in a wide arc and direct the resectoscope into the depths of a large prostatic fossa.

An O'Connor rectal drape is used to permit aseptic rectal manipulation which is essential in reaching all portions of the prostatic fossa for coagulation and resection when necessary.

It is wise to arrange the water conduit, light and power cords, and to check the function of the resectoscopic element before the abdominal incision is made, since there should be a minimum of delay between the removal of the prostate and the introduction of the resectoscope. A prolonged interval at such a time will permit the accumulation of clots within the prostatic fossa, obscuring the prompt localization of bleeding vessels.

The position of most comfort for the surgeon, facilitating the enucleation of the prostate, is at the foot of the table, standing between the patient's abducted lower extremities.

Each vas deferens is transected between ligatures. The bladder is exposed through a transverse suprapubic incision, and entered between two guide sutures. Intraurethral enucleation of the prostate is performed, and the gland extracted from the bladder. Digital palpation of the prostatic fossa determines complete removal of all obstructing tissue and a mental note is made of the localization of any residual adherent tissue which cannot be enucleated. A #30 Fr. sound is then introduced into the bladder per urethram to ensure its tolerance to the #28 Fr. Nesbit resectoscope. In some instances a meatotomy has been required, and in one case an external urethrotomy was necessary for the introduction of the instrument. Continuous intravesical suction is maintained throughout the endoscopic procedure which is performed with an open bladder.

Following passage of the resectoscope, fresh blood clot is displaced from the underlying tissue into the bladder with the aid of the cutting loop. An orderly and systematic inspection of the entire prostatic fossa is followed, usually beginning at 5 o'clock at the bladder neck, progressing counter clock-wise to 12 o'clock. One then returns to the posterior

midline position and rotates clock-wise to the anterior midline position. The major bleeders are found to enter at 5 and 7 o'clock, and fulgurated.

Careful attention must be given to the vesical neck which is found to be ragged from the blunt enucleation. It is often necessary to resect tags of mucous membrane from the neck to identify the bleeders.

In effecting hemostasis, only spot coagulation of arterial bleeders is carried out. It is well recognized that fulguration merely enlarges openings in the lumina of veins. Control of venous bleeding is left to compression by an inflated balloon catheter.

An important observation arising from this work has been the recognition in some cases of residual prostatic adenomata following a "so-called clean enucleation". Even where the operator has encountered no difficulty in creating a plane of cleavage between the adenomatous tissue and the surgical capsule, there have been a few instances where 5-8 Gm. of prostatic tissue have been resected. Certainly in the occasional instance where there is great difficulty in establishing a suitable cleavage plane, this technic has proved extremely useful, since such masses of tissue are readily resected. In such cases we have had to resect 13 and 19 Gm. after enucleating 40 and 50 Gm. respectively. This advantage applies similarly to the unsuspected case of prostatic carcinoma where no cleavage plane can be created. In one such instance a large carcinoma involving the anterior portion of the prostate was encountered and only a resection could be carried out. In this case 40 Gm. of tissue were resected.

The rough irregular appearance of the entire prostatic fossa following enucleation contrasts markedly with the smooth clean appearance of a well executed transurethral resection. Thus it has been found necessary to resect residual irregular projections of tissue to reach the underlying bleeding vessels for ultimate hemostasis.

When the surgeon is satisfied with the efficacy of his hemostasis, a #24 Fr. 100 cc. three way balloon catheter is introduced into the bladder. The balloon is inflated within the prostatic fossa to a sufficient degree to control venous bleeding. Proper positioning and state of inflation of the balloon are checked by intravesical and rectal palpation.

All fragments of resected tissue and blood clots must be removed from the bladder to avoid post-operative plugging of the catheter. The margins of the bladder incision are approximated temporarily with Alys clamps and the bladder irrigated to check the patency of the catheter and the color of the return irrigating fluid. Should the return fluid remain significantly sanguineous after a five minute period of observation, the catheter is removed, the resectoscope re-introduced, and the field re-observed. In the majority of instances the hemostasis is found satisfactory after the initial observation. The bladder incision is then closed in two layers using continuous sutures of 00 chromic catgut. A strip of Penrose cigarette drain is placed through the mid portion of the abdominal incision down to the line of bladder closure. The rectus muscles are approximated with interrupted sutures of 0 plain catgut. The anterior rectus sheath is approximated with interrupted sutures of #32 steel wire and the skin incision closed with interrupted fine silk sutures. The catheter is fastened to the patient's thigh under slight traction with adhesive tape to maintain the position of the inflated balloon within the prostatic fossa during the jouncing from the operating table, onto the stretcher, and ultimately into his bed. Although the arterial bleeding may be controlled accurately, premature dislocation of the balloon into the bladder may result in considerable venous bleeding with clot formation and bladder distention. The one patient in this series who required secondary hemostasis fell into this category.

With the patient in bed, a constant irrigation of distilled water, dripping at 30-40 drops/min. is attached to the catheter. This is maintained until the return is clear, a period on the average of 24-48 hours. In numerous instances the drainage is clear from the outset, indicating a minimal post-operative blood loss.

The patient is allowed out of bed on the first post-operative day, and the irrigation is discontinued temporarily at this time. The balloon is progressively deflated to a content of 15 cc. over a period of 48 hours.

The suprapubic drain can be shortened on the 3rd post-operative day, and removed on the 4th day. The skin sutures are removed on the 5th p.o. day. In general the catheter has been removed on the 7th p.o. day, but has been removed as early as the 4th day, with an excellent result.

Antibiotic therapy in the form of a depot type of penicillin and chloromycetin is continued throughout the first post-operative week.

As novices experimenting with this procedure, the duration of the operation varied from 90-120 minutes, but at present the average operating time is 60-70 minutes.

## RESULTS

	AVERAGE	MINIMUM	MAXIMUM
Post-operative Hospitalization (Days).....	12.7	9	24
Use of Indwelling Catheter (Days).....	7	4	10
Weight of Prostate Removed (Gms.).....	48.4	8	125
Healing of Suprapubic Wound			
Primary.....	56		
Leaked.....	6		
Infection.....	2		
Mortality.....	1		

From this chart it is observed: (a) that the average post-operative stay in this series was 12.7 days, with the shortest 9 days, and the longest 24 days. The latter prolonged stay was caused by a phlebothrombosis with pulmonary infarction. The local operative result, however, was excellent in that the patient voided well following removal of his catheter on the 7th p.o. day and enjoyed primary healing of his wound.

(b) The indwelling urethral catheter was maintained 7 days on the average, the shortest 4 days, the longest 10 days. The former was removed early due to intractable bladder spasms; the latter removed late because a diverticulectomy had been performed simultaneously with the prostatectomy. It is interesting to note that in one instance a ureterolithotomy was performed through a hockey stick extension of the transverse suprapubic incision in conjunction with the prostatectomy, resulting in primary healing of the wound with the patient voiding well on the 7th p.o. day.

(c) Glands of varying size have been removed by this method, the average being 48.4 Gm. The smallest was 8 Gm.; the largest 125 Gm. In the 8 Gm. removal, marked difficulty was encountered when attempting to introduce an instrument for resection into the bladder. It was deemed advisable to perform a cystotomy, and at the time of operation, a marked bladder neck contracture was found. The resectoscope was passed per urethram and guided into the bladder with the intravesical finger. The resection was carried out without further difficulty.

In several instances, although adenomata of moderate size were enucleated, a satisfactory cleavage plane could not be created to remove them in their entirety, necessitating resection of the residual tissue. Following enucleation of 50 Gm., 19 Gm. were resected; 40 Gm. followed by 13 Gm.; 25 Gm. followed by



12 Gm. In some cases, several grams of tissue were resected in removing ragged tags to secure hemostasis.

(d) In general, the wounds healed favorably with primary union the most common finding, despite the presence of pre-operative bladder infection in many cases. Following the removal of the Penrose drain, there usually was a scanty serous or seropurulent drainage for several days.

In 2 cases there was a mild fascial necrosis, but in only one of these was there suprapubic leakage of urine after removal of the catheter. We believe wound infection can be minimized by the surgeon changing his gloves just prior to closure of the wound, assisted by post-operative antibiotic therapy.

5 cases were considered unsuitable for a one stage procedure and had a preliminary cystotomy, followed by a second stage suprapubic prostatectomy with primary closure of the bladder. 4 of these patients had their catheters removed after 7 or 8 days with complete healing of their wounds having occurred. The fifth patient, an octogenarian, leaked suprapubically after removal of the catheter, requiring its reinsertion for a longer period.

#### COMPLICATIONS

There was 1 mortality in this small series. The patient was a 61 yr. old man in good health except for mild symptoms of coronary sclerosis. A competent cardiologist had adjudged him a suitable risk for a one stage procedure. The operation proceeded smoothly without alteration in the patient's blood pressure or pulse, and without significant blood loss. The operation lasted 60 minutes. He was seen by a member of the house staff two hours after the operation and all vital functions were found normal. The catheter was draining pink stained fluid. Fifteen minutes later the patient's nurse observed him to gasp and then cease breathing, with a concomitant cardiac standstill. Stimulants were to no avail. Permission for post mortem examination could not be obtained. Although this was an operative death, in all likelihood it was not directly related to the specific type of procedure employed.

One patient had a hemorrhage on the night of operation, resulting from displacement of the inflated balloon into the bladder, allowing venous bleeding to continue. Transurethral evacuation of blood clots was performed and no arterial bleeder was found. The catheter was replaced in the desired position, and the patient had an uneventful course thereafter. His catheter was removed on the 8th p.o. day, with primary healing of his wound.

A patient with polycythemia vera persistently oozed requiring a transurethral fulguration on the 6th p.o. day for hemostasis. 2 patients manifested a secondary hemorrhage on the 20th p.o. day necessitating transurethral hemostasis.

There were three instances of pulmonary infarction, all treated successfully with anti-coagulant medication.

In 6 instances there was suprapubic leakage of urine following removal of the urethral catheter. In 5 there was no further leakage after an additional 3 days of catheter drainage. The sixth patient had a previous cystotomy and leaked for a longer period.

In one patient the catheter failed to drain properly on the first p.o. day and urine leaked suprapubically. Although there was no apparent bleeding, he was given a spinal anesthetic to prepare for any contingency. Removal of the catheter revealed it to be obstructed by a fragment of tissue, and re-insertion of another catheter provided good urinary drainage, allowing its subsequent removal on the 8th p.o. day.

There were two instances of a unilateral funiculitis, and one of unilateral epididymitis, the latter occurring six weeks following operation.

One patient complained of slowing of his urinary stream and was found to have a large caliber stricture of his anterior urethra. This has responded to dilatations and permits passage of a #25 Fr. sound. Another patient, operated upon through an external urethrotomy, has developed a stricture of his penile urethra. This probably represents a peri-urethritis in response to the indwelling catheter.

One patient had stress incontinence which completely disappeared one month post-operatively. A second patient, has had persistent slight stress incontinence for about five months.

*Advantages* of this variation in the technic of suprapubic prostatectomy may be listed: (a) Dependable control of the bleeding which invariably occurs subsequent to enucleation of the prostate. (b) Removal of residual prostatic adenomata which frequently are overlooked in the conventional enucleation procedure. These may be causes for recurrent vesical outlet obstruction, both early and late. (c) Facile removal of prostatic adenomata in cases where a cleavage plane cannot be created between the adenomata and the surgical capsule of the prostate. This applies also to cases of unsuspected carcinoma of the prostate in which no cleavage plane may be found. (d) Transformation of the irregular prostatic fossa which may result from the usual enucleation procedure, into one free of ragged tags, enabling more rapid epithelialization with consequent rapid healing. (e) Primary closure of the bladder promotes shorter periods of post-operative hospitalization and also frees the patient of the encumbrance of a suprapubic tube and malodorous dressings.

#### SUMMARY

Experiences with a group of 63 cases in which suprapubic transvesical prostatectomy was performed are presented. Hemostasis was achieved by transurethral fulguration, thereby permitting primary bladder closure. The advantages of this technic have been indicated, and it is suggested as an excellent method for the removal of an enlarged prostate amenable to an enucleation procedure.

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# LIPOMYOSARCOMA OF THE KIDNEY\*

## REPORT OF TWO CASES

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Malignant kidney tumors of fat-forming cells are relatively uncommon. Only scattered single or small series of collected cases appear recorded in the literature. The scarcity of this type of tumor warrants reporting the following two cases together with a brief review of some of the pertinent facts on the subject.

### CASE REPORTS

*Case 1. History.* (Adm. #481806) S. M., a woman aged 46, was admitted to The Mount Sinai Hospital on November 14, 1941 for exploration of the left kidney for suspected tumor. She was first seen in January 1940 because of the presence of a palpable mass in the left upper abdomen. This mass was first detected by her family physician in September 1939 during the course of a routine physical examination following an automobile accident. A gastro-intestinal x-ray series at that time was negative. She had had one episode of painless hematuria of 48 hours duration about one month prior to the accident. A retrograde pyelogram taken December 27, 1939 showed the mass to be related to the left kidney and exploration advised (fig. 1). The patient, having lost her husband, a physician, at about this time, following an exploratory laparotomy for an obscure liver condition, decided against surgery. When seen by me in January 1940, she appeared in excellent health with no complaints other than the presence of an abdominal mass. Examination disclosed a large "grapefruit size" non-tender ballotable mass in the left upper abdomen. The centrifuged sediment of a voided specimen of urine showed an occasional white blood cell and rare red blood cell per high power field. An excretory urogram showed the upper half of the left renal outline poorly defined with some blunting and dilatation of the calyces to the upper pole. The right urinary tract appeared normal. Cystoscopic examination was entirely negative. A left retrograde pyelogram again showed deformity of the calyces to the upper pole and a poorly defined renal outline similar to December 27, 1939 (fig. 1). Surgery was advised but the patient decided to wait. She returned six months later because of an attack of pain in the left subcostal region. Abdominal palpation showed no appreciable change. The excretory urogram showed some increase in the deformity of the calyces (fig. 2). An x-ray of the chest was negative. A pyelogram taken October 17, 1941 showed an increase in calyceal deformity (fig. 3). In November 1941, approximately two years after the detection of the abdominal mass, the patient consented to surgical exploration.

*Examination.* On admission to the hospital the patient appeared in excellent health. Physical examination was essentially negative except for the presence of a ballotable non-tender mass in the left kidney region. The systolic blood pressure was 100, the diastolic 70. The interpretation of the excretory urogram was "tumor of left kidney".

*Laboratory data.* No significant findings were noted except for an occasional white blood cell and a rare red blood cell per high power field in the voided urine.

*Operation.* November 15, 1941, under Avertin-Ethylene anaesthesia, a nephrectomy was performed extra-peritoneally through a postero-lumbar incision including partial resection of the twelfth rib. A lobulated apparently encapsulated lipomatous mass about the size of "a small grapefruit" intimately connected with the lower pole of kidney was readily removed together with the kidney and surrounding perirenal fat.

*Pathological report.* "The specimen (fig. 4) consists of a left kidney together with a 9 cm. segment of not dilated, normal appearing ureter. The kidney itself measures 11 cm.

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\* From the Urological Service of The Mount Sinai Hospital, New York, N. Y.



x 6 cm. x 3.5 cm. However, bulging from the surface, particularly from the posterior aspect, are several large tumor masses, the largest measuring 12 cm. in diameter and coming off the outer lower posterior portion of the kidney. Smaller nodules measuring 5 cm. and 5.5 cm. in diameter arise from the upper and lower poles, respectively. In addition to these, there are a few (up to .9 cm.) nodules which protrude slightly from both the anterior and posterior surfaces of the organ. These large and small masses appear well demarcated from the surrounding renal parenchyma and the portions that extend outward from the kidney appear well demarcated by a thin-walled, translucent, in places, hemorrhagic capsule. The



FIG. 1. Left retrograde pyelogram, showing distorted calyces

largest tumor mass presents a bilobulated appearance. The surface is for the most part bright yellow. On cut section (fig. 5) it presents a uniform, fleshy, soft, golden yellow appearance except for a large, 3.5 cm. x 3.5 cm. area near the kidney surface which appears distinctly grayish yellow and is much firmer in consistency. The other tumor masses are similarly yellow in color for the most part but show an occasional small grayish, firmer area. On cut section, the kidney appears to be studded with numerous fairly well demarcated, similarly appearing nodules, the largest measuring 3.2 cm. in diameter. Some of these, in addition to the above described fleshy, yellowish appearance, present firmer grayish areas. There is a fairly clear demarcation between cortex and medulla. A considerable amount of normal appearing renal parenchyma is preserved. The pelvis of the kidney appears practically completely replaced by papillary-like fragments of the above-described

tumor tissue. Several of the intra-renal nodules form the base of these rough intra-pelvic projections. The hilus of the kidney, when viewed from the outside, does not appear unusual. There is no gross evidence of tumor in the large renal vessels."

*Microscopic Diagnosis:* "Lipomyosarcoma of kidney (fig. 6). (Diagnosis of sarcoma based upon infiltrating character of the tumor)."

*Post-operative Course.* Convalescence was uneventful, the patient leaving the hospital two weeks after operation. She is living and well nine and one half years after operation.



FIG. 2. Excretory urogram six months later, showing normal right renal pelvis and an increase in distortion of the left renal pelvis and calyces.

*Case 2. History.* (Adm. #557805) I. E., a woman aged 40 years, was admitted to The Medical Service of The Mount Sinai Hospital December 13, 1946 complaining of sharp intermittent pain in the left lower quadrant of the abdomen associated with nausea and vomiting of two days duration. She had low back pain for the past thirteen years.

*Examination.* On admission the physical examination disclosed dullness and diminished breath sounds over the left chest posteriorly and a large tender cystic mass in the left flank with moderate left costo-vertebral angle tenderness and lumbar muscle spasm. The systolic blood pressure was 125, the diastolic 80.

*Laboratory data.* The urine showed scattered white blood cells, 2-4 per high power field. The hemoglobin was 75 per cent and white blood cell count 8,600. The blood Wassermann was negative; the blood chemistry, normal. The excretory urogram showed an indistinct left renal outline with distortion of calyces to the upper pole. A cystoscopic examination



FIG. 3. Excretory urogram approximately 2 years after detection of abdominal mass, showing a normal right renal pelvis and marked distortion of the left renal pelvis and calyces.

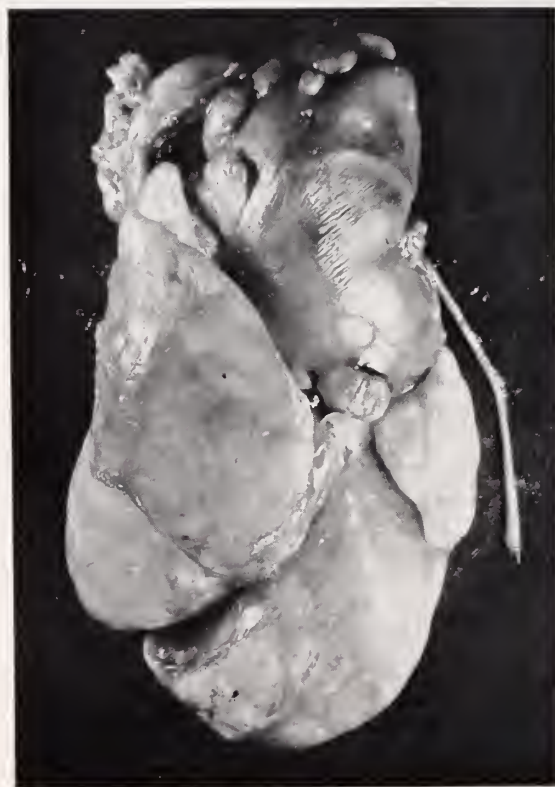
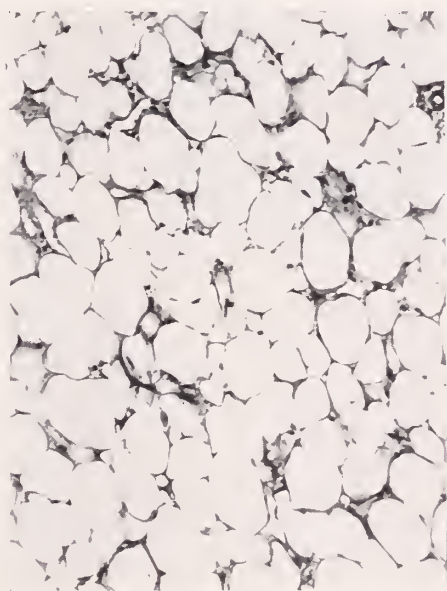


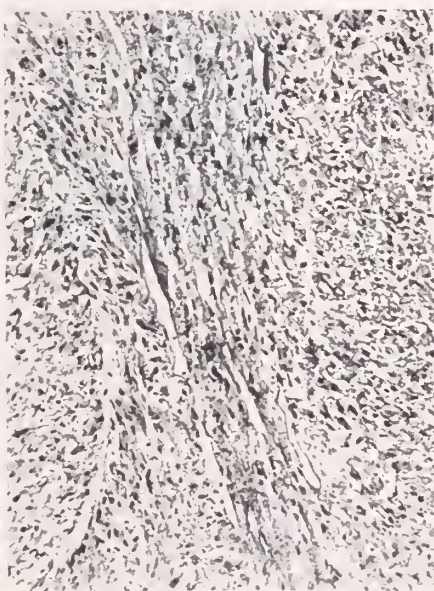
FIG. 4. Gross specimen, showing lipomatous masses with large lobulated mass arising from lower pole of kidney.



FIG. 5. Gross specimen opened longitudinally, showing lipomatous nodules within the kidney.



A



B

FIG. 6A. Microphotograph showing well differentiated adult fat cells. B. Microphotograph, showing myomatous tissue.



was negative. A left retrograde pyelogram showed calyceal distortion typical of renal tumor. An x-ray of the chest was negative. The patient was transferred to the Urological Service for operation.

*Operation.* December 17, 1946, under Ethylene anaesthesia, Dr. Lester (House Surgeon) through a left lumbar extraperitoneal approach, removed the kidney with a large lipomatous tumor involving its lower half.

*Pathological Report.* "Specimen (fig. 7) consists of left kidney completely surrounded by Gerota's fascia and its enclosed perirenal fat. The kidney itself weighs 450 gms., is markedly enlarged, deformed and elongated, measuring 20 cm. in length, 10.5 cm. in width, and 6 cm. in thickness. Almost the entire thickness of lower two-thirds is occupied by a sharply circumscribed, unencapsulated tumor measuring 12 cm. in length. It is composed

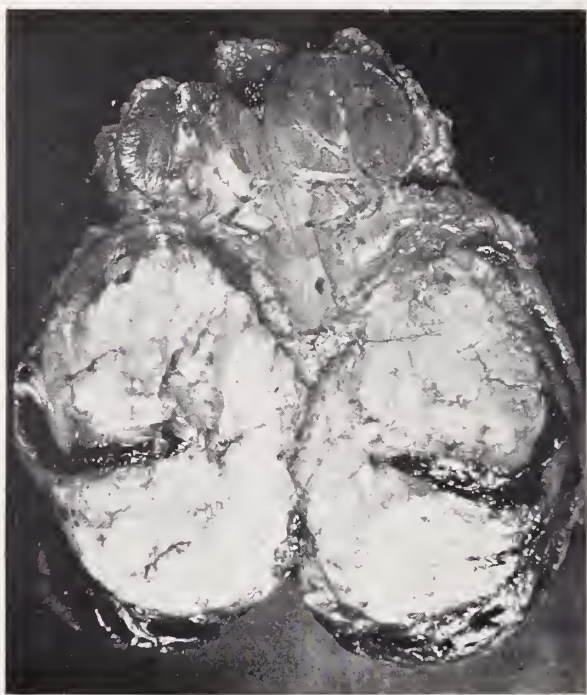


FIG. 7. Gross specimen, showing kidney with lower two-thirds occupied by tumor.

of soft, friable, bright yellow tissue which has the appearance of fat. Between the lobules of fatty tissue, pale gray firmer tissue is present. The tumor has produced marked thinning of the surrounding renal tissue and in the lower half of the kidney appears on both external surfaces as irregular bright yellow nodules. Focally, in the lower third of the kidney, there is a large irregular tear in the anterior surface. At this site there is extensive hemorrhage into the tumor. The capsule of the kidney strips readily. It is smooth and glistening and shows a dark purplish red discoloration. Focally, the tumor appears to infiltrate the capsule and the perirenal fat. All the perirenal fat is diffusely and extensively infiltrated by hemorrhage. Part of the pelvis and the lower calyces and major renal vessels are lost in the tumor. The ureter is of average calibre and does not contain blood. It cannot be stated with certainty to what extent these structures have been infiltrated. In the upper pole where the kidney is not infiltrated, it shows no gross change except for moderate pallor."

*Microscopic Diagnosis:* "Lipomyosarcoma of kidney".

*Post-operative Course.* Convalescence was uneventful, the patient leaving the hospital three weeks after operation. The patient, when last seen November 1949, approximately three years after operation, was apparently well but complained of pain in the left upper abdomen. There was no evidence of recurrence. An x-ray of the chest was negative. One taken of the dorso-lumbar spine showed minimal osteo-arthritis changes.

#### DISCUSSION

Liposarcoma in general is a comparatively rare type of tumor. Its etiology like other neoplasms is still unknown. An excellent paper on the subject by Stout, based on a study of 41 cases together with 134 cases previously reported in the literature, reveals some interesting facts: Unlike lipomata, which are more frequent in the female, liposarcomata affect both sexes about equally. They may occur at any age. The majority, however, appear within the fourth or fifth decade of life. Kretschmer's case was in a child two years old.

Liposarcomas have been recorded occurring in almost every region of the body, but seem to show a predilection for the retroperitoneal area, especially the perirenal portion, the mesentery, the omentum, in the thigh, popliteal space, and gluteal region. It is difficult to state how often liposarcomas develop from pre-existing lipomas. In all probability they are malignant from the start.

Seventeen cases of liposarcoma of the kidney have been recorded in the literature (4 by Fisher and one each by Froug, Harbitz, Hartwig, Lubarsch, McCartney and Wynne, Judd and Donald, Pearce, 3 by Weisel, Dockerty and Priestley, one each by Fish and McLaughlin, Tesler and Koiransky, and Newman and Reed). The two cases reported in this paper bring the total to nineteen (table 1).

The seven cases of Fisher, Froug, Harbitz, and Fish and McLaughlin occurred in individuals suffering from tuberous sclerosis and adenoma sebaceum (Pringle) of the face. No explanation is given for this rather bizarre association. Fisher, in his classical paper on the subject, in addition to liposarcomas, described other types of tumors in the kidneys of patients with tuberous sclerosis.

Liposarcoma of the kidney has no distinctive clinical symptomatology which differentiates it from other types of malignant renal neoplasms. The outstanding symptoms however are an abdominal mass and colicky pains occurring alone or in combination; the latter usually due to hemorrhage within the tumor. A positive or tentative diagnosis of renal neoplasm is usually based on the findings in the excretory or retrograde pyelogram.

Liposarcomas show a great variation both as to size and rate of growth, frequently attaining enormous proportions. Evidence seems to point to the "lipoblast" and not the fibroblast as the cell of origin. Stout regards the lipoblast "as an ordinarily specialized fat-forming mesenchymal cell which on occasion can produce a very wide variety of different and complex tissues". Murray and Stout have shown that they are readily distinguishable from fibroblasts.

Liposarcomas show a great tendency to be multiple and for that reason may simulate metastases. A case in point is the one reported by Lubarsch. His case had a large multinodular fibrous and fatty tumor in the left perirenal region with many smaller foci in the kidney itself, retroperitoneal region, suprarenal gland,

TABLE 1  
*Liposarcoma of kidney*

CASE NO.	AUTHOR	SEX	AGE	TUBEROUS SCLEROSIS	ADENOMA SE-BACCEUM FACE	SYMPTOMS	DURATION	CLINICAL DIAGNOSIS	TREATMENT	PATH. DIAG. KIDNEY	FOLLOW-UP
1.	Vogt* 1908	M	14	+	+	Epilepsy	Since birth	Brain tumor		Liposarcoma	Died—General dropsy
2.	Vogt* 1908	F	37	+	+	Epilepsy		Brain tumor		Liposarcoma	Died—cardiac failure
3.	Vogt* 1910	M	15	+	+	Epilepsy		Brain tumor		Liposarcoma	Died tuberculosis
4.	Fisher	M	16	+	+	Epilepsy; mentally defective	Since birth			Lipomyosarcoma	Died in an epileptic seizure
5.	Harbitz	F	38	+	+	Epilepsy since age 12			Exploratory celiotomy and biopsy	Hemangioliposarcoma	Died 6th day p.o., epileptic seizure. Metastases to liver
6.	Froug	F	30	+		Abd. pain; mass	Many years			Liposarcoma	Alive and well 1 yr.
7.	Hartwig	F	36			Enl. abd. abd. pain; collapse (few hrs pre-oper.)	8 yrs.	Kidney tumor	Nephrect. (loin incision)	Liposarcoma	Died 2 hrs. p.o. anemia, hemorrhage
8.	Lubarsch	F	62			—†	—	—	—	Lipoma; Lipomyoma; Lipomyosarcoma	

9.	McCartney and Wynne	F	37	Intermitt. abd. pain Severe abd. pain	6 wks. day of adm.	Kidney tumor	Nephrect. (loin incision)	Liposarcoma	Uneventful convalesc. post operative X-ray therapy
10.	Judd and Donald			—†	—	—	—	Liposarcoma	
11.	Pearse	F	53	Abd. mass	2 yrs.	Retroperit. tumor	Nephrect. (transperit.)	Liposarcoma	Well post operatively. No follow-up
12.	Weisel, Dockerty, and Priestley	M	68	Weakness; colicky abd. pain; mass; wt. loss	6 mos.	Kidney tumor	Nephrect. (transperit.)	Lipofibro-sarcoma	Alive and well 2 yrs.
13.	Case 1. Case 2			—†	—	—	—	Lipofibro-sarcoma	—
14.	Case 3.			—†	—	—	—	Lipofibro-sarcoma	
15.	Fish and McLaughlin	F	28	+ Abd. mass Recurrent abd. pain, fever, anemia	5 yrs. 2 yrs.	Kidney tumor	Nephrect. (loin incision)	Liposarcoma	Alive and well 2 yrs.
16.	Tesler and Korian-sky	M	67	Weakness, anorexia, loss of wt.	5 wks.	Hydro-nephrosis Nephro-lithiasis Kidney tumor	Not oper.	Liposarcoma Renal calculi	Died 5 wks. after adm. Metastases lungs, liver regional lymph node serous linings.



TABLE 1—Continued

CASE NO.	AUTHOR	SEX	AGE	TUBEROUS SCLEROSIS	ADENOMA SE- BACEUM FACE	SYMPTOMS	DURATION	CLINICAL DIAGNOSIS	TREATMENT	PATH. DIAG. KIDNEY	FOLLOW-UP
17.	Newman and Reed	M	37			Pain rt. costo- vertebral area, along iliac crest and region rt. hip.	2 days	Kidney tu- mor or cyst	Nephrect. (loin incision)	Liposarcoma	Alive and well 8 months
18.	Edelman Case 1.	F	46			Left upper abd. mass, transient left loin pain	2 yrs.	Kidney tu- mor	Nephrect. (lum- bar incision)	Lipomyosar- coma	Alive and well 9 yrs. 6 mos.
19.	Case 2.	F	40			L.L.Q. pain; nausea, vomit- ing; tender mass left flank	2 days	Kidney tu- mor	Nephrect. (lum- bar incision)	Lipomyosar- coma	Alive and well 3 years

\* Cited by Fisher.

† No case report or history given.

liver, heart, pleura, lung, periaortal and retroesophageal areas, spinal vertebrae and both femora. In spite of the benign appearance, he believed the small foci were metastases. This opinion is questioned because well differentiated or more malignant forms usually metastasize to the lungs, pleura, or liver. Stout was unable to find a single acceptable case with widespread metastases. In general, metastases seem to be less frequent than with other types of sarcoma.

Stout considers liposarcomas a single group of fat-forming tumors capable of manifesting different degrees of differentiation and makes the following subdivision:

1. Well differentiated myxoid type: This resembles the usual type of embryonal fat. The lipoblasts are rather small, regularly formed, capable of reproduction *in vitro* and although the tumors may be enormous, mitoses are absent. The tumor may recur locally but metastases are questionable.

2. Poorly differentiated myxoid type: The lipoblasts in this group are bizarre, often monstrous with variable nuclear formations, misshapen, often hyperchromatic or pyknotic and are incapable of reproduction *in vitro*. This type is definitely malignant, difficult to eradicate and may metastasize.

3. Round cell or adenoid type: These tumors are not myxoid, are difficult to eradicate and may metastasize.

4. Mixed group: These tumors are composed of two or more elements of the preceding groups. They, too, are definitely malignant.

The treatment of choice is early radical removal of the affected kidney together with the unruptured tumor and perirenal fat. The abdominal or transperitoneal approach and posterolumbar extraperitoneal route have been employed with about equal frequency. Pre- and post-operative x-ray therapy is of questionable value. It has been found useful in a few instances in treating small, easily accessible recurrent masses. The prognosis is dependent upon the operability and degree of differentiation of the tumor removed.

#### SUMMARY

Liposarcoma of the kidney is a rare tumor. Two cases have been added to the seventeen previously recorded. In each instance the tumor was of the well differentiated myxoid type, and not associated with tuberous sclerosis and adenoma sebaceum (Pringle) of the face. The outcome thus far has been favorable. X-ray therapy was not employed in either case. The first patient is now alive and well nine and one half years after operation and the second three years after operation.

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# PAPILLARY CARCINOMA OF THE URETER AND BLADDER THIRTEEN YEARS POST-NEPHRECTOMY FOR PAPILLARY CARCINOMA OF THE KIDNEY\*

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Papillary renal tumors, both benign and malignant, constitute 5 to 10% of all renal neoplasms. These tumors which arise from the pelvis and calyces, differ in several ways, from those of parenchymal origin. They also differ from sessile tumors of the renal pelvis and calyces. Sessile tumors are usually squamous cell carcinomata and carry the gravest prognosis.

Although the etiology of papillary tumors of the epithelium of the urinary tract [urothelium (Melicow)], is unknown, such tumors have occurred, following exposure to certain carcinogenic substances (phenanthrene, aniline dyes, etc.). Multiple occurrence of papillary urothelial tumors is a common finding. Whether this is explained by multicentric tumor foci, or by implantation metastasis from a primary growth, cannot be stated. Primary renal tumors are usually malignant. They are associated with concomitant, subsequent, or even antecedent ureteral and vesical tumors of a similar nature. Parenchymal tumors are rarely associated with similar tumors within the urinary tract, but are characterized by distant extra-urinary metastases, undoubtedly spread via the blood or lymphatic streams.

Hematuria is most often the presenting symptom of papillary urothelial neoplasia. The hematuria may arise from the implantation metastasis (multicentric focus) either in the ureter or in the bladder, as well as from the primary renal tumor. In a large number (33%) of the cases of renal papillary tumors, associated papillary lesions may be seen cystoscopically. Often it is the bladder lesion which causes the hematuria, but careful investigation of the upper urinary tracts is essential in such a case to determine whether the bladder lesion is primary, or secondary to an upper tract source. However, the primary renal lesion may be so small, that it cannot be detected by pyelography. On the other hand, parenchymal tumors (mainly clear cell carcinoma and adeno-carcinoma), in which hematuria is often a late symptom, usually present easily recognizable radiographic changes.

Because of the frequency of secondary ureteral and/or vesical foci or implants, the treatment of choice for papillary renal tumors is complete uretero-nephrectomy including the excision of the ureteral meatus with a collar of adjacent bladder wall. The necessity for ureterectomy is evident since 86% of all recurrences, or residual recurrences in papillary carcinoma of the kidney are found in the ureter or at the ureteral meatus. When the diagnosis of papillary carcinoma is reported only after nephrectomy, secondary ureterectomy is indicated. On the other hand, complete ureterectomy is not necessary in the operative therapy of parenchymal tumors.

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Although recurrences are usually evident within a year, the case to be described is of particular interest since a papillary transitional cell carcinoma was found in the ureteral stump and in the bladder thirteen years after a nephrectomy for papillary renal carcinoma. Whether this was a slowly growing original implant, or a manifestation of the "neoplastogenic" tendency of the urothelium can only be conjectured.

In general, the prognosis following nephrectomy for the type of papillary renal neoplasm under discussion, is appreciably better than in parenchymal malignant tumors.

#### CASE REPORT

*History.* (MSH #603125) S. G., a white man aged 40 years, was admitted to The Mount Sinai Hospital in June, 1935, because of severe left loin pain and hematuria of two days duration. His past history indicated that he was in good health until 1929 when he developed hematuria. At this time a bladder papilloma was fulgurated by an outside urologist. A biopsy report of the lesion was not available. About two years later, in 1931, he had an episode of transient hematuria and remained well until 1933 when he began having intermittent attacks of hematuria accompanied by back pain.

*Examination* on admission to the hospital was negative except for an enlarged, extremely tender left kidney. Intravenous urography showed the presence of a normal right upper urinary tract and an enlarged nonfunctioning left kidney. Cystoscopy was performed and catheters passed to both kidney pelves. Clear urine was obtained from the right side and bloody urine from the left. A left retrograde pyelogram revealed a deformity of the pelvis, dilatation of the lower calyces, and non-filling of the upper calyces.

*Course.* With a pre-operative diagnosis of left renal neoplasm, the patient was explored through a lumbar incision. The kidney was found to be enlarged by a tumor which involved the upper pole. A nephrectomy was performed with removal of 7 cm. of normal ureter. The pathology report was "Papillary carcinoma of the renal pelvis without infiltration. The ureter is uninvolved." The surgeon, at the time of operation, believed the lesion to be of parenchymal origin, and did not perform an ureterectomy. The post-operative course was uneventful and the patient was discharged on June 22nd, 1935.

He remained well until January, 1938 when painless hematuria recurred. The source of the bleeding could not be determined by cystoscopic examination. A catheter was passed up the stump of the left ureter but nothing was obtained on aspiration. A ureterogram was negative. Because of recurrent hematuria the patient was recystoscoped in July, 1938. Some bleeding was seen from the left ureteral orifice. A pinhead exerescence above the meatus was biopsied and reported as "normal bladder mucosa." Thereafter the patient reported to the followup clinic with recurrent episodes of hematuria, the source of which could not be determined. From 1941 until 1948 the patient failed to return to the follow-up clinic in spite of recurrent brief attacks of hematuria.

*Readmission.* The patient reentered the hospital in October, 1948, complaining of persistent hematuria of several months duration, associated with frequency, urgency, dysuria and nocturia. An examination was essentially negative except for the presence of a bladder distended by blood clots. Intravenous urography delineated a normal right upper urinary tract; there was no visualization on the left side, and a large filling defect was present in the bladder, mainly on the left side. Cystoscopic examination disclosed a large papillary tumor overlying the left side of the bladder, obscuring the left ureteral orifice. Biopsies of this tumor were reported as "fragments of edematous papilloma."

*2nd operation.* The pre-operative diagnosis, however, was papillary carcinoma of the ureteral stump and of the bladder and surgical intervention was carried out on October 22nd, 1948. Through a left modified Gibson incision an extraperitoneal exposure of the left ureteral stump was performed. The ureter was found to be markedly distended by tumor

and blood clots. It was mobilized down to its insertion into the bladder. The bladder was then opened and the vesical tumor was seen to arise from a narrow stalk running out of the left ureteral orifice. The entire ureteral stump together with adjacent bladder and bladder neoplasm were excised *in toto*. The bladder was closed around a cystostomy tube. The patient's post-operative course was marked by an episode of auricular fibrillation and a long period of suprapubic leakage. He was discharged on December 7th, 1948 for convalescent care.

*Pathology.* The operative specimen was an 18 cm. segment of ureter closed at its superior end and averaging 3.5 cm. in diameter (fig. 1). The ureteral orifice and a narrow rim of bladder was hidden by a pedunculated, soft, papillary neoplasm measuring approximately 3.5 cm. in diameter, whose pedicle arose from the lowermost ureter. Examination of the opened ureter disclosed the presence of blood clots and of a firm papillary mass 1.5 cm. in thickness and 4 cm. long, arising from the mucosal surface of the upper portion of the

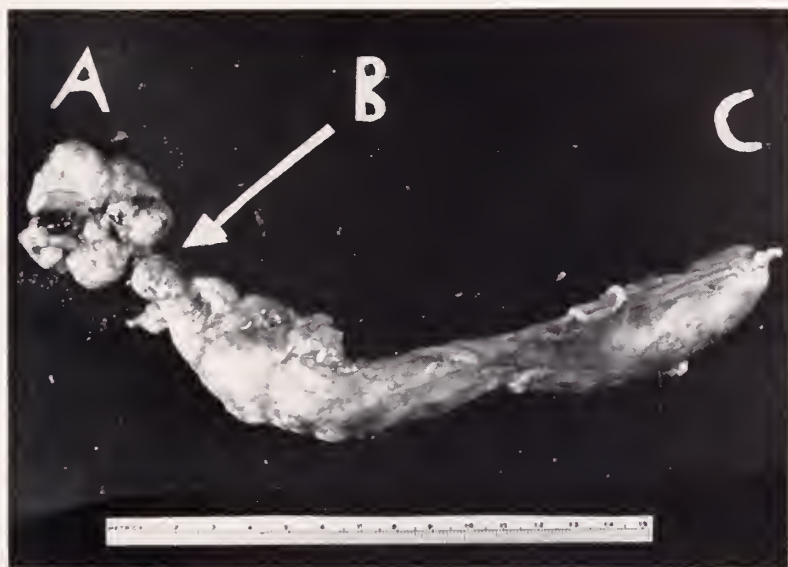


FIG. 1. Photograph of the unopened excised ureter. A.—Intravesical pedunculated papillary tumor. B.—Pedicle attached to area just within meatus. C.—Closed upper end of ureter.

ureter. Several smaller papillary excrescences were present in the distal ureter. The specimen was described as follows: "ureter showing infiltrating transitional cell carcinoma" indicating histologic findings often seen in portions of an infiltrating papillary carcinoma implying a higher degree of malignancy.

*Subsequent course.* Several weeks after discharge, the patient was readmitted because of a draining suprapubic vesico-cutaneous sinus. This healed after removal of a fibroadenomatous prostate gland by transurethral resection.

In the latter part of 1949 the patient had no urinary symptoms but did have minor discomfort from a large incisional hernia. Investigation of the etiology of a chronic cough disclosed an anterior mediastinal mass. After radiotherapy proved ineffectual, he was admitted to the surgical chest service where a benign thymoma was removed without incident.

#### SUMMARY

A case is described to illustrate the locational and chronological multiplicity of papillary tumors of urothelium.

A small bladder papilloma antedated a demonstrable kidney tumor by six years. The long interval of thirteen years between a primary nephrectomy for papillary carcinoma of the renal pelvis and the secondary ureterectomy for a similar neoplasm is noteworthy.

The presence of a large intravesical pedunculated tumor arising from the lowermost ureter is another striking clinical feature.

Nephro-ureterectomy including the ureteral meatus and adjacent bladder is again advocated as the treatment of choice for papillary carcinoma of the renal pelvis or calyces.

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# CONGENITAL ECTOPIC HYDRONEPHROTIC KIDNEY SIMULATING AN INTRAPERITONEAL LESION

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Not infrequently lesions of the urinary tract present symptoms and physical findings closely resembling those caused by disease of intra-abdominal structures. Congenital ectopic kidney, for example, often the site of surgical disease, may be incorrectly diagnosed as acute appendicitis, large bowel tumor, mesenteric cyst, or give rise to abdominal symptoms of unclarified origin. That urography can be of inestimable value in the elucidation of obscure symptoms is well illustrated by the case herein reported.

Congenital ectopia may be homolateral or crossed, fused or unfused. The condition undoubtedly arises from an abnormal early vascular fixation of the kidney. In the normal embryological development the kidney ascends and simultaneously rotates on its longitudinal axis; by the 5th month, the upper pole of the kidney is at the level of the 11th rib; the normal renal blood supply at the level of the 2nd lumbar vertebra is established between the 8th and 9th week. Prior to the latter period the kidney anlage is supplied by vessels more caudally situated, the persistence of which accounts for many cases of renal ectopia. The blood supply of ectopic kidneys is usually from adjacent large trunks—just above or at the bifurcation of the aorta, from the iliacs, the middle sacral, or inferior mesenteric arteries. Occasionally an ectopic kidney, as in the case to be cited, will considerably displace the intestines, interfering with the function of the bowel and producing intestinal symptoms.

## CASE REPORT

*History.* I. O. (M. S. H., #607047). A Puerto Rican little girl aged 3 years, was brought to the pediatric service because of a protuberant abdomen, right lower quadrant abdominal pain after bowel movement, and constipation. She had been previously hospitalized at the age of 4 months for constipation and abdominal distress. X-rays taken at that time were reported as revealing redundant and slightly dilated large bowel. Between the first and second admissions, the patient was observed in the Out-Patient-Department for the same complaints. Her development had been normal and she had gained weight. On several occasions various diagnoses were entertained, from Hirschsprung's disease to mesenteric cyst, cyst of the ovary, to a mass of urinary origin.

*Examination.* The child was adequately developed and well nourished with a markedly protuberant abdomen. The blood pressure was 96 systolic and 64 diastolic. The liver was palpable 1½ cm. below the costal margin. A doughy, soft mass, dull to percussion, completely filled the subumbilical portion and right half of the abdomen and was well defined when examined under general anesthesia; the soft cystic mass could also be felt on rectal examination.

*Laboratory findings.* Urine, blood and stool examinations were negative. Culture of the urine from the right kidney showed no growth. The Mantoux Test was 1:10000 positive. X-ray examination of the chest was negative. Barium enema showed no evidence of an organic intrinsic lesion of any portion of the large bowel; the proximal large bowel was incompletely outlined since the patient was unable to retain further injection of the enema.

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However, there was evidence of extrinsic pressure on the sigmoid and hepatic flexure from a large mass or masses in the lower abdomen and in the right flank; the entire small bowel was displaced into the left upper quadrant; there was no evidence of megalocolon (fig. 1). Intravenous pyelography outlined the pelvis and calyces of the right kidney fairly satisfactorily; no gross abnormality was noted except for displacement of the right kidney which was unusually high and in a slightly horizontal position; the right ureter showed marked lateral bowing in the middle of its course. No definite visualization either of the kidney outline or of the urinary tract could be demonstrated on the left side; there was a smooth impression on the superior and right aspects of the partially filled bladder (fig. 2).



FIG. 1. Barium enema depicting displacement of the descending colon and sigmoid with the absence of filling of the ascending colon by an extra-colonic mass.

*Cystoscopy and left retrograde pyelography*—the bladder, both ureteral orifices, sphincter margin and posterior urethra were negative; indigo carmine appeared in good concentration in 10 minutes from the right kidney; a catheter was passed up the left ureter to a distance of 15 cm.—35 c.c. of clear urine were aspirated; no indigo carmine appeared from the left kidney during a 45 minute period of observation; the retrograde pyelogram showed the tip of the left ureteral catheter overlying the region of the right sacro-iliac articulation; the injected Hippuran outlined a giant-sized, dilated kidney pelvis and calyces measuring about 10 cm. in diameter and occupying the right side of the abdomen and subumbilical region; the appearance was that of a crossed ectopia of the left kidney with huge dilatation of the pelvis and calyces. Preoperative cystography was negative (figs. 3 and 4).

*Operation.* Ten days after the second admission (on February 17th, 1950), the patient was operated upon. A trans-peritoneal approach rather than the left lumbar was decided upon in the belief that the blood supply to the left kidney, usually anomalous, would for the most part arise from the right side of the main blood vessels. Through a right paraumbilical



FIG. 2. Intravenous pyelogram demonstrating pelvis and calyces on the right side displaced upwards, the ureter bowed laterally. No excretion of dye to correspond to a left kidney



FIG. 3. Left retrograde pyelogram—antero-posterior view outlining giant hydronephrotic ectopic left kidney. The ureter courses across the midline to the right lower sacral region.



FIG. 4. Same as Figure 3—oblique view



FIG. 5. Post-operative intravenous pyelogram—24 days after nephrectomy, demonstrating the normal position of the right visualized upper urinary tract. Normal bladder outline.

muscle-splitting incision, the peritoneal cavity was entered. The cecum, appendix and right kidney were found situated underneath the liver. The small bowel was displaced to the left side of the abdomen by a huge, hydronephrotic, L-shaped left ectopic kidney which occupied the right side of the abdomen and ran across the midline over the promontory of the sacrum to the lower left quadrant of the abdomen. The right lateral leaf of the posterior parietal peritoneum was incised and the kidney partially mobilized. After packing off the peritoneal cavity, the hydronephrotic sac was aspirated of 800 cc. of clear, watery fluid. Further mobilization was continued. There were two sets of blood vessels, one running from the second portion of the duodenum to a caput of thinned-out renal parenchyma at the upper pole, the second from the aorta just above its bifurcation. There were no aberrant vessels at the uretero-pelvic junction. The ureter entered the dependent portion of the hydronephrotic sac which sagged below the point of entrance of the ureter into the pelvis. The ureter was of normal calibre. Nephrectomy was performed, the retroperitoneal space was drained with Penrose drains behind the sutured right leaf of the parietal peritoneum. The appendix was removed in typical fashion.

*Pathology report.* "Specimen is a huge sac-like kidney from which the fluid had been removed. It weighs 68 grams and the renal tissue which is present at one pole appears irregularly atrophic and occasionally scarred. Coarse lobules, apparently foetal in origin, are present. The kidney measures 8 cm. in length, the width of the kidney substance itself, about 3 cm. The hugely distended pelvis appears smooth but irregularly hemorrhagic. The calyces are markedly distended. On section, the cortex of the renal parenchyma is unusually narrow in some areas, and almost vanishes at one point. Only at the opposite pole does the cortex obtain the usual thickness. A few tiny serous cysts up to 3 mm. in diameter are found in the more atrophic renal pole. Diagnosis—left ectopic kidney located on the right side, showing hydronephrosis."

*The post-operative course* was uneventful. A check-up intravenous pyelogram showed the right kidney to be of normal size, shape and position; the right upper urinary tract and urinary bladder outlines were normal (fig. 5). The child was discharged from the hospital 24 days after the operation.

#### SUMMARY

A 3 year old female child, admitted for the second time to the pediatric service with abdominal symptoms and signs, consisting of a protuberant abdomen, right lower quadrant pain and constipation, was found on barium enema to have displacement of the large and small bowel by an extrinsic mass. At first, various diagnoses were entertained such as Hirschsprung's disease, mesenteric cyst, cyst of the ovary, and finally a mass of possible urinary origin. However, urologic investigation revealed the true nature of the illness, namely, a huge hydronephrotic crossed ectopic left kidney. A trans-peritoneal nephrectomy was followed by an uneventful course.

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## PULMONARY DECORTICATION IN CIVILIAN PRACTICE\*

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Decortication of the lung apparently was first performed by Fowler, in a case of empyema thoracis, in 1893. The procedure enjoyed considerable popularity for a time but, during the next twenty years, gradually fell into discard. A half-century after Fowler performed his first decortication, the procedure was revived by Burford during World War II. The latter author and his associates (32-34) found it so effective in the treatment of organizing hemothorax, that other military surgeons quickly adopted it as a routine method of dealing with certain types of traumatic hemothorax—both infected and uninfected—that failed to respond to conservative measures within a period of 6-8 weeks. (In this connection, on the basis of personal experience, we (39) can attest to the excellent results that were obtained with the operation in the European Theatre of Operations.) Despite the convincing demonstration of the value of pulmonary decortication during the War, there have not been a great many reports (6, 10, 16, 17, 18, 22, 23, 25, etc.) concerning the use of the procedure in civilian practice. Although cases amenable to such treatment are not too common during peace-time, we have encountered a sufficient number during the past few years to lead us to the conclusion that pulmonary decortication has earned a permanent place in the armamentarium of the civilian surgeon. Accordingly, it is our purpose to report the cases which we have treated since the end of the war, in the hope that surgeons who previously have not employed the method may be encouraged to apply it in suitable cases.

During the period from January 1946 to January 1950, we have performed 12 pulmonary decortications for a variety of conditions. In each instance, regardless of the varying etiology, the basic pathologic abnormality found at operation consisted of a partially or totally collapsed lung which was prevented from re-expanding by a well-defined organized membrane which enveloped it more or less completely and was reflected from the surface of the lung onto the adjacent diaphragm and parietal pleura (fig. 8). In our cases, the intrapleural dead-space contained various types of material. Thus, in certain instances, it was filled with sterile blood; in others, it contained thin, brown fluid and masses of fibrin in various stages of organization. In some cases, the fluid was milky infected; in others, it was grossly purulent. In a number of instances, the intrapleural dead-space contained both air and fluid (hydropneumothorax, hemopneumothorax or pyopneumothorax) (fig. 8). Finally, in certain cases, the lesion consisted of a chronic pneumothorax in which the lung was prevented from expanding as a result of its encasement by an organized membrane of the type already described. Thus, it is apparent that the cases fell into several general types.

In three of our cases, the lesion was a traumatic clotted hemothorax associated

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with multiple fractures of the ribs. In one of these, the injury had occurred four years previously and the existence of a chronic clotted hemothorax had gone unrecognized until the patient sought admission to the hospital because of increasing shortness of breath. There was one case of clotted hemothorax due to a perforating injury of the left chest by a bullet. The resulting lesion was identical with many which we had encountered during the War. In two cases the patient had sustained a stab wound of the chest. One occurred ten months previously; the other six weeks previously. In the first case, following the injury, the left pleural cavity became filled with blood. Treatment consisted of repeated thoracenteses followed by instillation of penicillin. The pleura became infected, as evidenced by the changing character of the pleural fluid and the development of septic temperature; but the same type of treatment was continued for the entire ten months prior to the patient's admission to the hospital. In another case, the lesion was an empyema that occurred in sequence to a splenectomy. In two instances, the lesion was a spontaneous hemopneumothorax. One occurred following a severe bout of coughing; the other after lifting a heavy object. In two cases, the patients had pulmonary tuberculosis that was treated by the induction of pneumothorax. In each instance, after pneumothorax therapy had been discontinued, the lung failed to re-expand and the patient was left with a chronic pneumothorax. In both cases, the small amount of fluid that was present in the pleura became infected and pyopneumothorax developed.

The following case of traumatic clotted hemothorax resulting from a "closed" injury is reported in detail in order to illustrate some of the characteristic clinical, diagnostic and therapeutic aspects of the condition.

#### CASE REPORT

*Case History.* C. H. a man aged 52 years, was admitted to the Beekman-Downtown Hospital on May 29, 1947 shortly after falling 22 feet, from a ladder to the deck of a tug-boat, while climbing up the side of a ship. In falling, he landed on the posterior aspect of the left chest and shoulder. On admission to the hospital, x-ray examination of the chest at the bedside revealed multiple fractures of the left fifth to twelfth ribs inclusive. There was no evidence of subcutaneous emphysema, pneumothorax or hemothorax (fig. 1). The left chest was strapped and the patient placed on parenteral penicillin therapy. The course was uneventful for the first three days. However, on the fourth day following admission, the patient suddenly complained of severe pain in the left chest and rapidly went into profound shock. Because of the sudden onset of pain, in a patient who previously appeared to be progressing satisfactorily, and the pallor, profuse perspiration and evidence of peripheral circulatory failure, the diagnosis of coronary occlusion was made. However, an electrocardiogram failed to substantiate the clinical diagnosis and, accordingly, the patient was treated by intravenous infusion of blood and electrolytes. He responded satisfactorily and, on the following day (June 3, 1947), another x-ray film of the chest was made (fig. 2). This revealed the presence of an extensive shadow over the left chest which had not been present when the patient was admitted to the hospital. The trachea now was markedly displaced toward the right. The left chest was aspirated, but only 10 cc. of blood was obtained. The clinical manifestations and the findings on x-ray examination suggested that the patient had suffered a severe hemorrhage into the left pleural cavity. The fact that only 10 cc. of blood could be obtained on aspiration, in retrospect, suggested the diagnosis of clotted hemothorax. During the next five weeks, the left chest was aspirated periodically and varying amounts of bloody and subsequently thin brown fluid were removed.



FIG. 1. C. H. Bedside film made on admission to the Hospital. Note fractures of ribs on left side but absence of fluid in left chest.

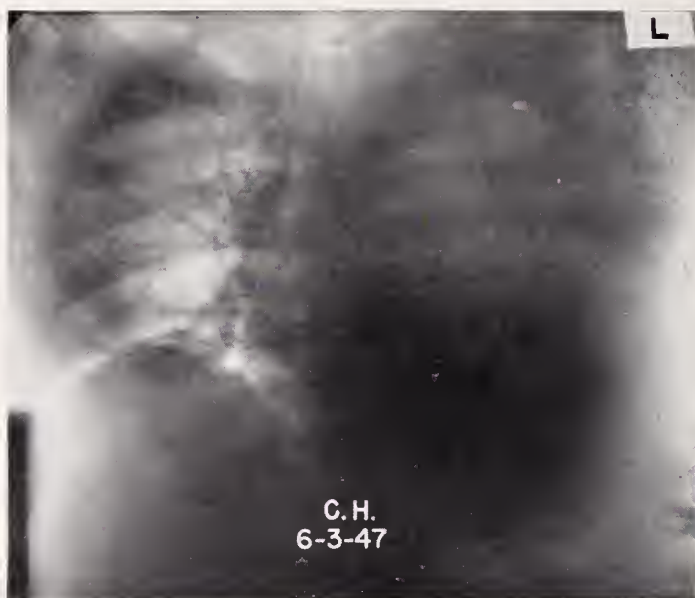


FIG. 2. C. H. Bedside film made 5 days after admission. Note the dense shadow now present over the left chest and the deviation of the trachea and heart toward the right side.

At no time, was the amount of fluid that could be aspirated very great. Furthermore, despite repeated aspirations, the shadow overlying the left lung field remained essentially unchanged in extent. In addition, the heart and trachea now were displaced toward the left side and the intercostal spaces on the latter side narrowed to an appreciable degree.

On July 14, 1947, approximately  $6\frac{1}{2}$  weeks after injury, one of us (A. S. W. T.) saw the

patient in consultation. At that time, the left chest was retracted and its motion obviously restricted. Dyspnea was present at rest and was increased considerably on walking. The temperature was irregular and ranged up to 101° F. X-ray examination, made shortly before we first saw the patient (fig. 3), revealed elevation of the diaphragm, narrowing of the intercostal spaces, deviation of the heart and trachea toward the left, and a dense shadow over the left chest. On the basis of the clinical history, physical examination and x-ray films, the diagnosis of clotted hemothorax was made and operation advised.

*Operation.* On July 23, 1947 (55 days after injury), under intratracheal ether-oxygen anesthesia, operation was performed by one of us (A. S. W. T.). With the patient in the right lateral recumbent position, a postero-lateral incision was made over the seventh left intercostal space extending from the posterior axillary line to the paravertebral region. The seventh and eighth ribs were divided close to the transverse processes. The left hemi-



FIG. 3. C. H. Film made approximately 6 weeks following admission. Note that extensive shadow remains over left chest. Trachea and heart still are deviated toward the left. Intercostal spaces (left) are narrow, and left diaphragm is elevated.

thorax was entered in the seventh intercostal space and a rib spreader introduced. When the latter was opened, the left hemithorax was found to be filled with masses of soft, dark brown, grumous material and collections of thin brown fluid which were separated from one another by fibrinous septa. After the various loculations had been broken down and the contents of the chest completely evacuated, the hemithorax was found to be lined by a grayish-red, firm membrane which was reflected from the thoracic wall over the diaphragm and then onto the surface of the mediastinal pleura which overlay the heart and the collapsed left lung. The membrane over the surface of the lung was incised and a plane of cleavage, between it and the lung, was entered. The membrane then was peeled progressively, by sponge dissection, from the lung, pericardium, and diaphragm. It varied in thickness from  $\frac{1}{4}$  to  $\frac{5}{16}$  inch. At a number of points, it was so adherent to the underlying lung that no plane of cleavage could be found. In these areas, small rents were inadvertently made in the pulmonary parenchyma. These were immediately closed with catgut sutures. After the membrane had been removed from the lung, pericardium and diaphragm, positive pressure was applied by the anesthetist through the intratracheal tube; the lung expanded immediately and filled the hemithorax completely. Penicillin, 200,000 units in



60 cc. of saline solution, were instilled into the pleural cavity. The latter was drained by means of two large catheters, one introduced through the tenth intercostal space posterolaterally and the other through the fifth intercostal space in the anterior axillary line. The two catheters were connected, by means of a Y-tube, with a single drainage tube which in turn was attached to an underwater drainage system (40). Steel wire sutures were used to approximate the divided rib ends; the wound was closed in layers with catgut sutures. Whole blood, 1,000 cc. was administered during, and immediately after, operation. This was followed by glucose in saline in adequate amounts. Parenteral penicillin, 50,000 units, was administered every three hours. A film made on July 28th (5 days after operation) disclosed marked clearing of the left chest. The heart and trachea were in normal position and the left diaphragm no longer was elevated (fig. 4).

On the sixth post-operative day, both drainage tubes and the skin clips were removed; the wound appeared clean. On the day of operation, the temperature rose to 103° F. but gradually fell to normal by the tenth day. On August 2, 1947, the patient complained of



FIG. 4. C. H. Film made 5 days after operation. Note marked clearing of left chest. Heart and trachea are now in normal position. Left diaphragm is at normal level. Drainage tubes are in situ.

sudden thoracic pain which was assumed to be due to a small pulmonary infarct. At the time of discharge, on the 19th postoperative day, the lung was practically completely re-expanded and breath sounds could be heard clearly over the entire left chest.

The fluid obtained at operation was sterile, whereas that aspirated on June 17th (6 days preoperative) was reported to contain a hemolytic staphylococcus albus. The pathologic report of the membrane which had been removed was as follows: "proliferative pleural reaction. Well advanced granulation tissue, and terminal scar with atelectasis of underlying parenchyma."

Six weeks after operation September 6, 1947, (fig. 5) the left chest was entirely clear. When last examined in January, 1949 (17 months post-operative) the patient was completely asymptomatic.

#### ADDITIONAL CASES SUMMARIZED

*Case 2.* W. N., a man aged 27 years entered The Mount Sinai Hospital on February 16, 1946, three weeks after suffering a right-sided spontaneous hemopneumothorax. Closed

thoracotomy and multiple aspirations of the chest had been performed at another hospital, prior to admission, without improvement. On February 17, 1946 thoracotomy, evacuation of blood clot, decortication of the lung and suture of the causative pulmonary laceration were performed. Nineteen days after operation the patient was discharged, the last x-ray examination revealing a small amount of residual fluid in the right pleural cavity. Subsequent follow-up examinations disclosed complete restitution of function and a normal roentgenogram of the chest.

*Case 3.* S. C., a 13 year old boy, suffered a "stove-in" left chest in a railway accident  $4\frac{1}{2}$  weeks before entering The Mount Sinai Hospital. Emergency treatment had been rendered at another hospital. On admission to our Hospital, multiple rib fractures and a hemopneumothorax were present. On March 2, 1946, a left thoracotomy was performed. Considerable old blood clot was found and evacuated; decortication was performed. Five



FIG. 5. C. H. Film made 6 weeks after operation. Note complete clearing of left chest

severely-fractured ribs with depressed fragments were exposed, elevated, and then fixed by means of wire sutures. The chest was closed with drainage. The post-operative course was smooth. On March 18, 1947, the patient was asymptomatic and both lungs were well aerated. When seen recently, the patient was completely well, and an x-ray film revealed no abnormality.

*Case 4.* J. H., a man aged 25 years, suffered a stab wound of the left chest 10 months prior to admission to The Mount Sinai Hospital. Hemothorax, followed by chronic empyema, resulted. Operation was performed on January 12, 1946. Thickened pleura was encountered, the lung being collapsed and completely bound down by a firm fibrous membrane. Infected, necrotic fibrin masses and pus were present. Decortication was performed but, because of unusual adherence of the membrane to the lung at several points, the lung was entered here and there. The lung was re-expanded and the chest closed with two-tube drainage. A residual empyema developed and required thoracotomy with rib resection on February 13, 1946. The patient was discharged from the hospital on March 16, 1946, with a small, residual, clean cavity. Unfortunately no follow-up visits were made by this patient, but we assume that the small cavity (capacity 35 cc.) closed without incident.



FIG. 6. B. H. Early tuberculosis lesion at right apex prior to induction of pneumothorax

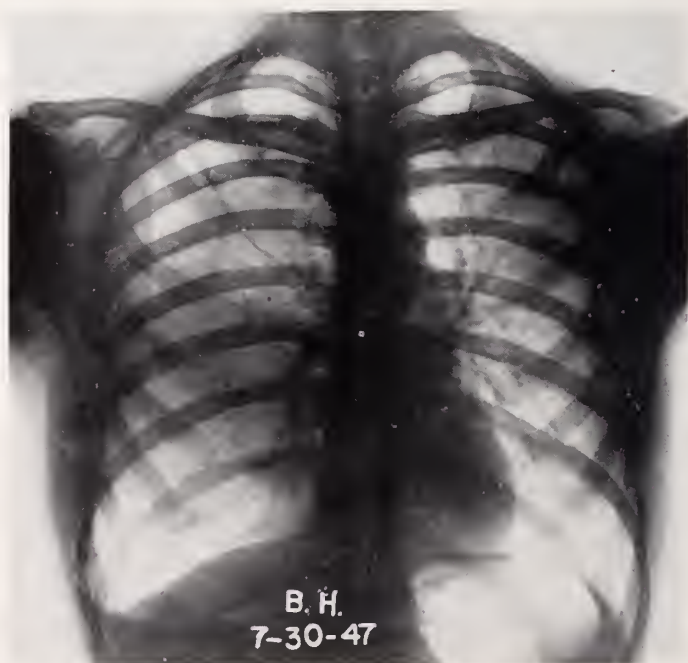


FIG. 7. B. H. Note partial collapse of right lung following pneumothorax therapy. No fluid present in pleural cavity.

*Case 5.* B. H., a 24 year old woman, had an early tuberculous lesion at the right apex (fig. 6). This was treated by pneumothorax (fig. 7). Pneumothorax was maintained for 16 months. High fever then supervened. Six weeks before admission to The Mount Sinai Hospital, culture of fluid in the right chest yielded a staphylococcus aureus. Because of the presence of an unexpanded lung and fluid in the chest, which remained infected despite the use of large doses of penicillin and streptomycin (parenterally and intrapleurally), decortication was proposed (fig. 8). On September 18, 1947 the right lung and diaphragm were decorticated; a membrane  $\frac{3}{4}$  of an inch thick was removed. The lung re-expanded readily under positive pressure; the chest was closed with two-tube drainage. X-ray films taken 2 days post-operatively revealed only a small collection of fluid and air in the right



FIG. 8. B. H. Case of pyopneumothorax, occurring as a late complication of pneumothorax therapy for pulmonary tuberculosis. Note the well-defined, organized membrane which prevents re-expansion of the right lung, as well as pus and air in the intrapleural dead-space.

chest (fig. 9). Subsequent x-rays disclosed complete re-expansion of the lung; no infiltration was noted in the parenchyma (fig. 10). Last follow-up in the latter part of 1949 revealed the patient to be asymptomatic and the chest to be clear.

*Case 6.* E. S., a 57 year old woman, was admitted to the Doctors Hospital on May 8, 1948 because of an unexpanded right lung which followed pneumothorax therapy for tuberculosis. One-and-a-half years previously, pneumothorax had been induced with apparent cure. Seven weeks before admission, pleuritic pain and fever developed. On May 12, 1948, operation was performed. The right lower, right middle and part of the right upper lobe were decorticated. Cultures of fluid at operation were reported "sterile". The lung was re-expanded and the pleura drained. Post-operative course was entirely satisfactory; the patient was discharged on the nineteenth postoperative day. The patient has been followed up to the present and has remained entirely well.



*Case 7.* T. W., a 14 year old boy, was admitted to The Mount Sinai Hospital after suffering a through-and-through gun shot wound of the left chest five weeks before admission. Intrapleural hemorrhage and clotted hemothorax developed. On May 15, 1946, thoracotomy was performed. The lung which was collapsed and covered by a beefy-red exudate, was decorticated. A bullet-tract was noted in the upper and lower lobes. Several loose indriven rib-fragments were found and removed. The diaphragm then was decorticated. The thorax was drained. The post-operative course was uneventful. The wound healed *per primum*, the patient being discharged in 11 days with the lung re-expanded. The patient failed to report to our Follow-up Clinic.

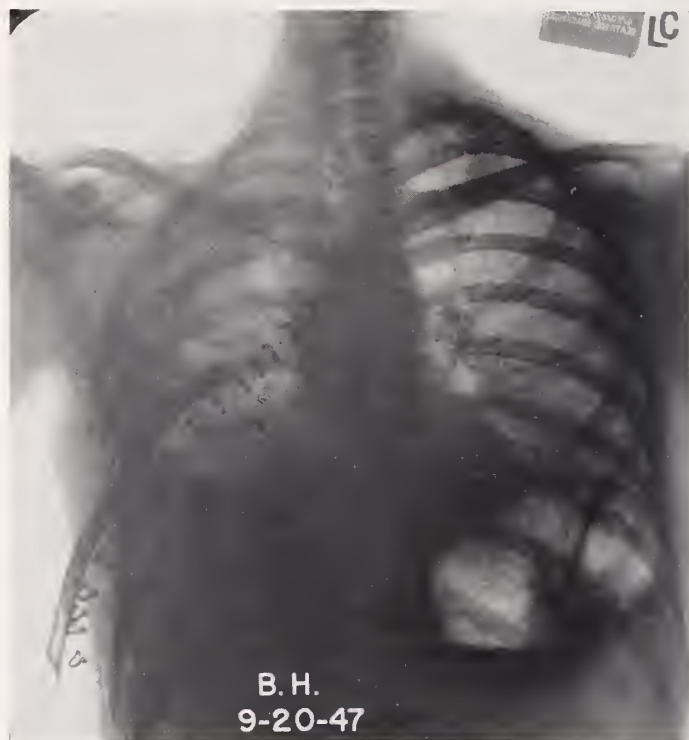


FIG. 9. B. H. Two days post-decortication. Drainage tubes in situ. Note small amount of air and fluid in right pleural cavity.

*Case 8.* G. K., a 44 year old man, suffered a "steering wheel injury" to the right chest in 1943. On March 17, 1948, he was admitted to The Mount Sinai Hospital because of an extensive shadow in the right chest and marked dyspnea. The diagnosis of "fibrothorax", secondary to chronic clotted hemothorax, was made. At operation, the lung was found collapsed and covered by a thick fibrous membrane. Dissection of the membrane from the lung was extremely difficult. In performing decortication, the extremely adherent lung was inadvertently entered at several points. Under positive pressure, the lung re-expanded but did not make complete contact with the chest wall. Empyema developed and was drained on April 14, 1948. The lung re-expanded slowly and, in order to hasten obliteration of the intrapleural dead space, modified thoracoplasty was performed on June 28, 1948. On January 24, 1949, x-ray examination revealed the chest to be clear and the patient to be asymptomatic.

*Case 9.* H. H., a 39 year old woman, developed a left hemothorax with infection follow-

ing splenectomy for an undiagnosed blood dyscrasia. Five months later, on October 20, 1948, exploratory thoracotomy was performed. A membrane,  $\frac{3}{4}$  inch thick, was removed from the lung and diaphragm. The lung when inflated was noted to fill the chest completely. The post-operative course was complicated by peripheral neuritis and nutritional edema. Recent follow-up examination revealed a completely satisfactory result, the chest wound being healed and the patient free of pulmonary complaints.

*Case 10.* M. N., a 32 year old man, suffered a spontaneous hemopneumothorax on October 23, 1948 while at work. He was treated by thoracotomy and drainage and "attempted" decortication three weeks later, at another Hospital. This was followed by high fever and the development of an obvious empyema. Five weeks later he was admitted to The Mount Sinai Hospital in a severely debilitated state with pus draining from a thoracic drainage tube. On January 15, 1949 he was operated upon. Pus was evacuated from the chest. The

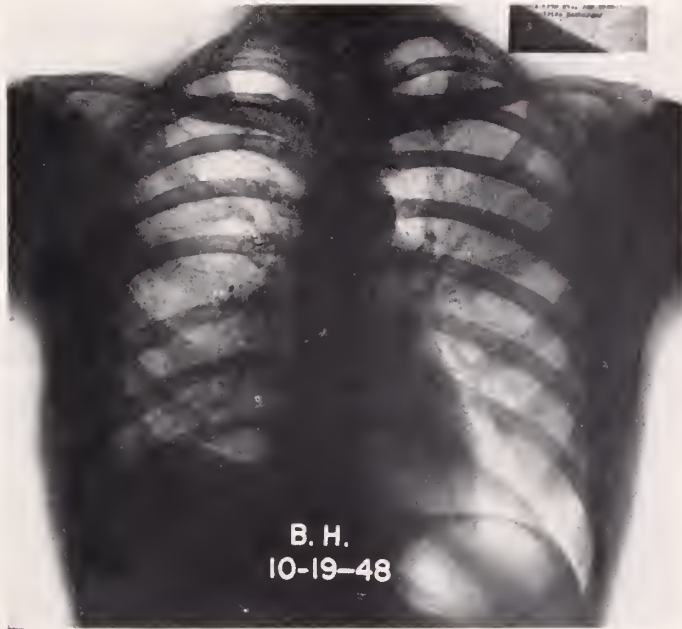


FIG. 10. B. H. Complete re-expansion of lung, no parenchymal lesion present. Note wire sutures holding ribs in perfect approximation.

lung was collapsed, bound down and covered by a firm, fibrous membrane. Decortication was performed. Blebs were noted in the upper lobe and several air leaks at the sites of tears which were made in the lung, were closed by suture. The lung expanded well under the influence of positive pressure exerted by the anesthetist. However, following operation, a small empyema necessitated further decortication and multiple rib resections. Three months post-operatively (May 14, 1949), a small clean cavity remained. Since the latter showed little tendency to close after 6 months of observation, the patient was re-admitted to the Hospital. On November 11, 1949 the wound was revised, the cavity unroofed and the edges of the wound sutured. Thereafter, the wound healed rapidly. The patient left the Hospital entirely well. When last seen on May 15, 1950, he was well.

*Case 11.* L. K., a 56 year old white man experienced sharp pain in his left chest after lifting a heavy object in August of 1949. The pain radiated to the back, became more severe on exertion and was accompanied by mild dyspnea, cough and wheezing. Roentgenogram revealed fluid in the left chest. Bronchoscopy on October 20, 1949 revealed obstruction of

left lower lobe bronchus. Biopsy and smears for carcinoma cells were negative. The pleural fluid failed to disclose any growth on culture. No tumor cells were found. On November 23, 1949 operation was performed. There was a large amount of clear fluid in the lower posterior portion of the pleural cavity with blood clots on the diaphragm. There was no evidence of tumor. Decortication was proceeded with and the lung completely re-expanded under positive pressure. Two-tube drainage was employed. Post-operative course was entirely satisfactory. At follow-up examination on January 16, 1950 the patient was asymptomatic. Roentgenogram on January 17, 1950 disclosed a very small amount of fluid at the left base. The lung was completely re-expanded.

*Case 12.* S. I., a 34 year old Negro was admitted on January 3, 1950 because of pain in the right chest, dyspnea and hemoptysis. Six weeks prior to admission, he had been stabbed in the right anterior chest, hospitalized in another hospital and discharged in two days. Two weeks later he developed pulmonary symptoms. Roentgenogram disclosed an infra-pulmonary collection of fluid and atelectasis of the right lower lobe. At operation on January 4, 1950, an infra-pulmonary empyema was drained; and it was noted that the right lower lobe was collapsed and bound down by a thick membrane. Decortication of the lobe was complete and the lung re-expanded without difficulty. Roentgenogram on January 14, 1950 revealed diminution in the pleural exudate. The right lung was completely expanded and the right leaf of the diaphragm was considerably elevated. Patient was discharged asymptomatic, but failed to report to our Follow-up Clinic.

#### DISCUSSION

The cases reported herein demonstrate the value of pulmonary decortication in a variety of lesions encountered in civilian practice. Whenever the lung is collapsed and bound down by a membrane, whether this is associated with clotted hemothorax (with or without inflammatory reaction) or following pneumothorax (whether spontaneous or induced), the lung can and should be released by decortication. The presence of empyema is no contraindication to the procedure, since infection often can be controlled by antibiotics. The membrane covering the lung and diaphragm should be removed as completely as possible, whereas the membrane lining the thoracic parietes usually can be left *in situ* unless it is extremely thick and restricts the motion of the thoracic parietes to a great degree. Endotracheal anesthesia is invaluable, both in maintaining adequate oxygenation during operation and in re-expanding the lung after decortication. Small air leaks which occur not infrequently in cases of clotted hemothorax of relatively long duration, as a rule, seal over rapidly with closed drainage. Two-catheter closed drainage, without suction, has proved eminently satisfactory. One catheter should be inserted high anteriorly and the other low posteriorly. Removal of drainage catheters should be carried out only when fluid ceases to drain, or bubbling of air stops. Furthermore, the post-operative roentgenograms should indicate complete expansion of the underlying lung. Intra-pleural and parenteral penicillin should be administered freely. Rapid and complete re-expansion of the lung is the goal of treatment. Decortication may be carried out as soon as the diagnosis of clotted hemothorax is made. In this connection, it should be stressed that in cases even of as long as four years duration, satisfactory-reexpansion can be accomplished. The application of decortication to post-pneumothorax cases (following collapse therapy) may restore to normal many lungs which formerly were destined to remain permanently functionless.

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## PNEUMONECTOMY FOR PRIMARY LOCALIZED LYMPHOMA\*

ARTHUR H. AUFSES, M.D.

The differentiation between the several types of diseases of lymphoid tissue is occasionally difficult. At times, the pathologist cannot classify the disease in any special category but must be content with an all-inclusive term, lymphoma.

Reviews of many large series of cases have shown that although the lymphoid diseases are usually generalized, there is an occasional case in which the disease remains localized, at least for a period of time. The absolute localization of such disease can only be proven through long standing observation and finally by a postmortem examination, or by its surgical removal, without later recurrence. The literature contains a number of reports on localized primary lymphosarcoma of the gastrointestinal tract, without recurrence after surgical removal. Usually, the first clinical evidence of lymphoid disease is found in the lymph nodes. Occasionally, these nodes may represent metastatic deposits from a small primary focus in a neighboring organ. Even at postmortem, it may be impossible to determine the primary site.

The lungs are rarely the primary site of lymphoblastoma. Sugarbaker and Craver (1), in a review of 196 cases of lymphosarcoma, reported one patient in whom the primary lesion may have been in the lung, but the mediastinal nodes were also involved. Vieta and Craver (2), in an analysis of 239 cases of lymphosarcoma, stated, "To date we have not seen an example of primary lymphosarcoma in the lung proper." Falconer and Leonard (3), in an analysis of 25 cases of lymphosarcoma and 30 cases of lymphatic leukemia state, "No cases were found in our present study where clinical and pathologic evidence suggested inception of the disease in the parenchyma of the lung."

It is not surprising, therefore, to find only three other reported cases of patients with primary lymphosarcoma or lymphoid disease localized to the lung who have remained apparently cured after resection of the neoplasm. Churchill (4), in 1947, reported the successful resection of a malignant lymphosarcoma, lymphocytic type, of the upper lobe. The patient had complained of chills, fever, and pain in the chest. Radiotherapy was given after operation and the patient was alive and well six months later. The gross description of the lesion was so similar to that of the case reported here, that it is of interest to quote—"The entire upper lobe is filled with a tan translucent homogeneous infiltrate which is especially prominent about the blood vessel walls, and bronchi, and which does not seem to destroy the normal lung markings."

In the same year, Spatt and Grayzel (5), reported the resection of a primary lymphosarcoma of the lung in a patient who had had hemoptysis as the predominant symptom, and who was alive and well fourteen months after operation.

Maier (6), in 1948, reported the case of a patient, upon whom a pneumonec-tomy was performed in 1944 for a primary lymphosarcoma of the lung. Nineteen

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months later, a nodule appeared in the remaining lung. Radiotherapy was administered, followed by the disappearance of what appeared to be a metastasis. The patient was alive and well three years after operation. As in our case, the disease was discovered accidentally during fluoroscopic examination performed because of gastrointestinal symptoms.

Churchill's patient was given radiotherapy, which may very well have stopped the growth of any other intrathoracic foci. The follow-up in his case was only six months. Maier's patient developed a secondary focus as late as nineteen months after operation. Our patient did not receive radiation therapy, and has remained free of disease for thirty-one months. Were other lesions present at the time of operation, one would expect clinical symptoms to have become manifest by this time.

#### CASE REPORT

*History.* E. J.—(Adm. 565219), a housewife entered The Mount Sinai Hospital on April 29, 1947 for the first time. She complained of abdominal pain for one year. The pain appeared after the ingestion of food and was relieved by powders. It became worse at night but was absent in the morning. Six weeks before admission, she had a gastrointestinal series performed. This was negative but during the fluoroscopy, the roentgenologist noticed a shadow in the right upper lung field. Because of the thoracic finding, she was advised to enter the hospital, but delayed doing so until she developed a dull, pressing pain in the right posterior chest. At no time did she have any cough or expectoration, nor any other symptoms referable to her lungs. Except for a hysterectomy and unilateral oophorectomy performed in October, 1944, the remainder of her history was negative.

*Examination.* The patient was a well developed woman apparently in good general condition. The salient features were confined to the chest; there was slight dullness, bronchial breath sounds, and increased voice and whisper, with occasional râles on deep inspiration over the right upper chest, anteriorly, posteriorly and in the axilla. There was no lymphadenopathy. The blood pressure was 170 mm. systolic and 90 mm. diastolic.

*Laboratory data.* Urinalysis was negative. The hemogram revealed the following: hemoglobin, 88 per cent; white blood cell count, 6850, with leukocytes, 61 per cent; lymphocytes, 36 per cent; eosinophiles, 2 per cent.

*Roentgenographic examination* of the chest performed on April 14th in the Out Patient Department, revealed "a circular density about 3 cm. in diameter in the region of the right hilum. An atelectasis of the right upper lobe is noted. The appearance is most likely that of a pulmonary neoplasm with right upper lobe atelectasis."

*Bronchoscopic examination* performed in the Out Patient Department two days before admission to the hospital, revealed a distortion of the right upper lobe bronchus without definite intrabronchial pathology. A specimen of tissue removed from this bronchus for biopsy was reported as acute and chronic in-

flammation. In an attempt to obtain a better view of the bronchus, an artificial pneumothorax was induced, and a 50 per cent collapse was obtained. At a second bronchoscopic examination, on May 8th, a better visualization of the right upper lobe bronchus was obtained, but the branch bronchi could not be seen. A specimen taken from the depths revealed no tumor.

Sectional roentgenography performed on May 5th was reported as follows: "The bronchial branches extending upward from the root of the right lung are normal in calibre. These extend above a triangular shadow and appear to arise from a right upper lobe bronchus, which is not narrowed. The triangular shadow is best demarcated on sections made further back, suggesting that it represents the collapsed posterior portion of the right upper lobe. The rounded density ad-

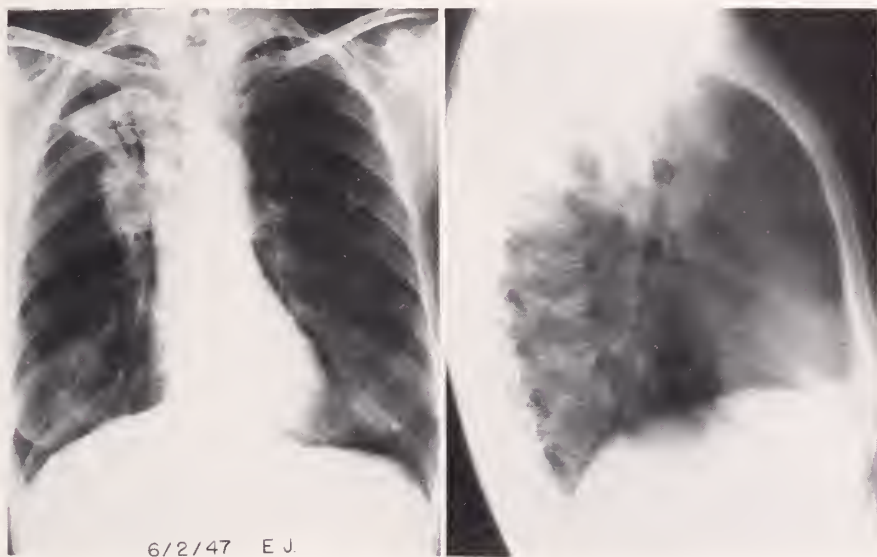


FIG. 1. Roentgenograms showing shadow at the root of the right lung with a triangular density extending into the upper lobe. (6/2/47)

jacent to the mediastinum just beneath the root of this shadow appears, at this examination, to represent a mass at the root of the lung between the upper and lower lobe bronchi, rather than a dilated pulmonary artery."

*Course.* In the belief that a neoplasm of the lung was present, the patient was advised to have an exploratory thoracotomy. She refused surgical intervention, and left the Hospital on May 20th, to return six days later, complaining of anterior chest pain and nausea, and consented to operation.

Before operation, another sectional roentgenography was performed more posteriorly and this revealed, "The triangular density in the posterior portion of the right upper lobe contains a number of small areas of increased aeration that are oval in shape and whose axis is directed towards the root of the lung. The appearance is that of bronchiectasis within the collapsed posterior segment



of the right upper lobe. In addition, more anteriorly, there is seen, at this time, a quite distinct oval mass, situated between the right upper and lower lobe bronchi, measuring one and one-half inches in length and three quarters of an inch in width. This suggests the presence of a large lymph node."

*Operation.* On June 7th, under nitrous-oxide-oxygen-ether, intratracheal anesthesia an incision was made in the third anterior interspace. The pectoralis major muscle was divided and the pleural space entered. The third and fourth costal cartilages were cut across and the internal mammary vessels ligated and cut. A rib spreader was inserted and the pleural cavity and its contents visualized. The right upper lobe was rather densely adherent over its anterior aspect. The upper lobe was freed from the chest wall, and was found to be the seat of a diffuse lesion, extending outward from the hilum and crossing the fissures to involve a small area of the apex of the lower lobe and the middle lobe. The pathologic appearance of the lesion seemed to be inflammatory rather than malignant.

A wedge shaped piece of the diseased area was removed for frozen section. On the cut surface the lung did not appear to be the site of malignant disease. But the pathologist reported that the specimen was unusual and contained many round cells, and that it was probably a malignancy. The mediastinum was carefully inspected, and no adenopathy could be found. A pneumonectomy was then performed. The superior and inferior veins were doubly ligated, transfixed, and cut across. The pulmonary artery was treated in a similar manner. The bronchus was freed and sectioned close to the carina. Its stump was closed with a double layer of interrupted silk sutures and allowed to retract into the mediastinum. The mediastinal pleura was then closed. Penicillin, 500,000 units, was placed in the pleural cavity, and the thorax was closed with pericostal chromic catgut sutures to the ribs, interrupted silk to the muscle, superficial fascia, and skin. The patient received 1500 cc. of blood during the operation and a bronchoscopy was performed while she was still on the operating table.

*Pathologic examination, gross:* "The specimen is a resected right lung which weighs 330 gms. All three lobes are collapsed. The upper lobe shows thickening of the pleura which is partly fibrous and partly due to infiltration by moderately soft tannish nodules. In places the pleura is torn. At the apex of the upper lobe, there is a subplurular scar. The lobe is almost completely replaced by a fleshy mass which is poorly circumscribed and leaves only a thin rim of collapsed lung tissue where it does not infiltrate the pleura. The mass measures approximately 8 cm. in its largest diameter. On its cut surface, it shows a glistening pale tan tissue which appears rather cellular and poor in stroma and is traversed by small areas of anthracotic pigment. The bronchi pass through this tissue without being narrowed and without showing changes in the mucosa. Pleural involvement is most marked near the hilum. The middle lobe, which is likewise collapsed, is apparently adherent to the upper lobe due to infiltration through the pleura from the adjacent mass. Near the hilum, there is infiltration with the same type of tissue seen in the upper lobe, while the remainder of the lobe is grossly

free of tumor. The tumor tissue appears to infiltrate the pulmonary parenchyma without involving vessels and bronchi. The lower lobe is also collapsed to a large extent. Its pleura shows prominent lymphatics and at the apex there is an area of fibrous thickening. Near the hilum, the pleura is again infiltrated by the tumor which extends into the lung tissue for a short distance from the hilum. Here again, the bronchi appear uninvolved. The hilar lymph nodes are soft and anthracotic and do not appear involved."

*Microscopic:* "There is a diffuse infiltration of the pulmonary parenchyma by small mature lymphocytes. The cells are uniformly regular and there are no

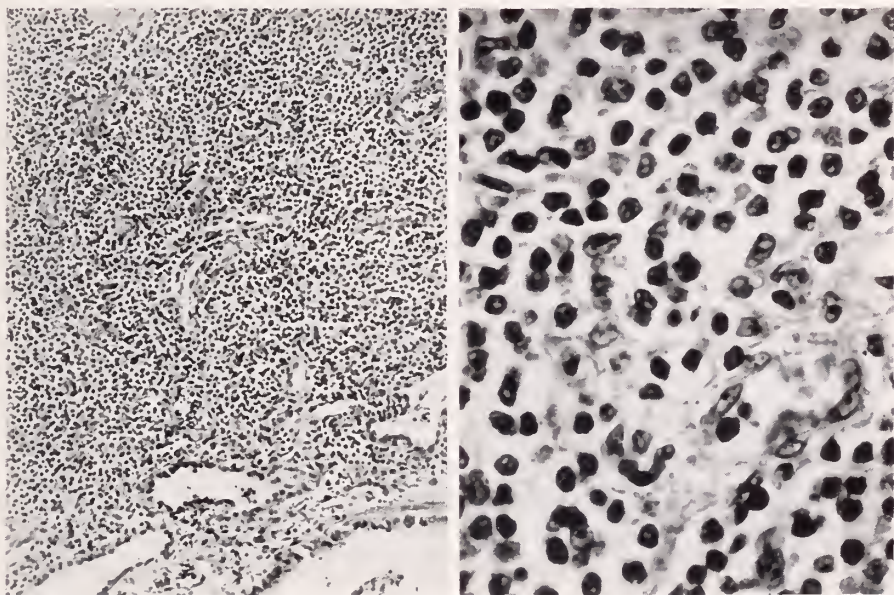


FIG. 2. Low and high power photomicrographs showing diffuse infiltration by small mature lymphocytes. The cells are regular and there is no mitosis. The blood vessels and bronchi are not involved.

mitoses to be seen. The lumen of the blood vessels and bronchi are not invaded by the infiltrative process. Pathologic diagnosis: Lymphoma of the lung."

*Postoperative course.* The first five days were uneventful. On May 12th, her skin was found to be covered with a maculoerythematous eruption, and on May 13th, auricular fibrillation occurred. This was controlled within twenty-four hours by the administration of quinidine. On May 14th, 300 cc. of air and 120 cc. of sero-sanguineous fluid were removed from the right pleural cavity. Bacteriologic examination of the fluid revealed no organisms. On May 20th, 300 cc. of fluid were removed and this also was negative on bacteriologic examination. On July 1st, the patient began to complain of severe headaches and her temperature, which had been normal immediately postoperative, had gradually risen to 101°F. daily. Ophthalmoscopic examination was negative.



FIG. 3. Postoperative roentgenogram (12/2/47)

A bone marrow aspiration on July 1st was reported to show the following:

Megakaryocytes.....	22%
Myeloblasts.....	0.4%
Promyelocytes.....	0.4%
Myelocytes N.....	8.8%
Myelocytes E.....	2.0%
Non-segmented.....	23.6%
Segmented.....	24.0%
Segmented E.....	3.2%
Lymphocytes.....	2.0%
Plasma cells.....	1.6%
Erythroblasts.....	0.8%
Reticulum cells.....	0.4%
Normoblasts.....	22.8%

A lumbar puncture, performed on July 3rd, revealed an initial pressure of 10 mm. of water and a final pressure of zero. The highest pressure on coughing was 70 mm. of water. The spinal fluid contained: protein, 46 mg. per cent; sugar, 55 mg. per cent; and chlorides, 866 mg. per cent.

An electroencephalogram was performed on July 9th. It showed a fair amount of diffuse and symmetrical 4-6 per second activity appearing without focal accentuation. The impression was: "A slight degree of diffuse cerebral dysfunction as occurring in numerous conditions, e.g., diffuse cerebral processes, metabolic disorders, etc. There is no indication of a focal lesion, in particular, a tumor of the cerebral hemispheres."

The headaches gradually disappeared, and the temperature returned to normal at the end of three weeks. The patient was discharged in good condition on July 10th. She has been seen in the Follow-Up Clinic at regular intervals, the last time, in January 1950. She has remained perfectly well and her only complaint has been some dyspnoea. Roentgenogram of the chest reveals the left lung to be normal, the right pleural cavity filled with post-pneumonectomy exudate and the mediastinum displaced to the right. There has never been any lymphadenopathy.

#### SUMMARY

A patient with a primary localized lymphoma of the lung is described. The disease was accidentally discovered during roentgenography of the gastrointestinal tract. Pneumonectomy was performed, with apparent cure, as the patient is well thirty one months after operation.

I wish to thank Dr. Sadao Otani for the preparation of the photomicrographs and for the description of the pathologic findings.

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## EXTRAPLEURAL PULMONARY RESECTION (PLEUROPNEUMONECTOMY)

IRVING ARTHUR SAROT, M.D., F.A.C.S.

Involvement of the pleura frequently complicates pulmonary disease. The two most serious complications are extensive and dense pleuropulmonary adhesions, and pleural infection (empyema). In the past, the inability to overcome the serious technical problems occasioned by those complications has limited the feasibility of pulmonary resection.

In tuberculosis, particularly, and in chronic lung abscess and other pulmonary suppurations, the difficulties in resection caused by the presence of pleural symphysis served, for many years, to keep pulmonary extirpation from achieving its present acceptance as a form of therapy. Not infrequently operations which had been begun to remove a lung had to be abandoned because the lung could not be separated from the chest wall; or the operations were so prolonged by dissection through dense adhesions, and manipulation of the lung so great, that operative shock was frequent, anesthetic difficulties due to spillage of secretions common and postoperative spreads of disease not unusual. Rupture of adherent cavity walls and incision of diseased parenchyma or pleura were frequent sources of contamination.

A second limiting factor was the teaching that pleural infection or empyema was a contraindication to pulmonary resection (1). Many patients with pulmonary disease suitable for such treatment have been denied resection because associated empyema was present. In other cases, excisional procedures already begun were not completed because of the unexpected operative finding of an empyema.

Although Tuffier (11) had as early as 1888 resected a tuberculous apex of a lung extrapleurally, and Fowler (2) in 1901 had noted the importance of removing the entire diseased pleura in empyema, these isolated observations were ignored because of a universal reluctance to damage or remove the parietal pleura surgically. This reluctance was based on the accepted belief (3) that under no circumstances should the parietal pleura be removed, especially in tuberculosis, since its removal would permit the spread of infections to tissues beyond.

### THE EXTRAPLEURAL APPROACH

Since 1936, I have utilized Maurer's (4) technique of enucleating, extrapleurally, broad pleuropulmonary adhesions encountered during closed pneumolysis and have noted (9) its many advantages. Application of this principle to lobectomy and pneumonectomy has made it possible to circumvent the difficulties in dissection occasioned by dense and widespread adherence of the lung and to excise an empyema with the diseased part of the lung.

Extrapleural dissection is of particular value in approaching the hilus. When the hilar area is exposed extrapleurally (fig. 1) through a posterior mediastinal approach, the thickened pleura with its adhesions is by-passed and the hilar

structures are exposed in a region relatively uninvolved by disease. It has been my experience that the connective tissues about the bronchus and the pulmonary vessels in the mediastinum are not usually involved to any great degree by the inflammatory processes of the lung and pleura. Pleural involvement even in most extensive empyemas is predominantly costal and diaphragmatic (fig. 2).

The extrapleural approach to the hilus avoids difficult dissection through matted nodes since the greatest degree of lymph node involvement in inflammatory states is usually at the bifurcation of the main bronchus, distal to the region in which the bronchus is exposed. The intratracheal nodes and the peribronchial nodes of the main bronchus have usually separated from the bronchus quite easily if the peribronchial connective tissue sheath was incised and the bronchus freed within it. The division of the bronchus at the carina, the suturing

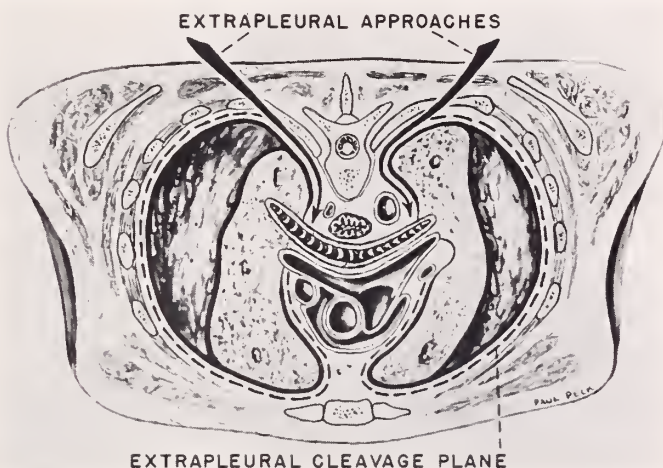


FIG. 1. Diagrammatic sketch illustrating the posterior extrapleural approach  
(By courtesy of the Editors of *Thorax* and the British Medical Association.)

of the proximal end and the ligation of the vessels are achieved in an unobstructed and clean field. The lung with the adherent pleura or, if any empyema is present, with the entire empyema sac, is then freed by an extrapleural dissection and removed (fig. 3).

The widest application of the technique of extrapleural resection has been in pulmonary tuberculosis (7) in which cases with complete pleural symphysis or empyema, previously considered inoperable, have now become suitable for resection. Tuberculous or mixed empyema, with or without bronchopleural fistula, previously a most difficult condition to control or cure especially when complicated by underlying active parenchymal tuberculosis, can now be treated successfully by extrapleural pulmonary resection and pleurectomy, with a mortality and morbidity rate no greater than that in resections for uncomplicated pulmonary tuberculosis (8). Extrapleural resection has thus become important in the surgical treatment of pulmonary tuberculosis, extending the indications for resection, lessening complications and improving results.

As the scope of application of pulmonary resection has been enlarged in the treatment of pulmonary and pleural inflammatory and neoplastic processes, it



FIG. 2. The mediastinal aspect of a tuberculous lung which has been removed with the empyema by extrapleural pneumonectomy and total pleurectomy. The empyema is seen not to extend mediastically nor, in this particular case, to the base of the lower lobe, nor to the diaphragm. This photograph presents dramatically the line of fusion between the parietal pleura and the visceral membrane of the empyema as an almost-circular line extending about the mediastinal aspect above the hilus. The freedom of the mediastinal aspect from severe pleural adhesions is characteristic.

has become inevitable that concepts and ideas previously accepted should be reexamined.

Tchertkoff and Selikoff (10) first pointed out that extrapleural resection which began as a technical convenience achieved a greater effect, at least in tuberculosis, by removing the parietal pleura. This membrane has no useful function after

pneumonectomy and its removal eliminates its great secretory and reactive power and any foci of pleural tuberculosis. Its hypothetical function as a "limiting membrane", preventing the spread of infection to the mediastinum and extrapleural tissues, can apparently be dispensed with since the source of infection has been removed. The pleura is very prone to become infected when contaminated, but the extrapleural tissues seem to be more resistant to infection.

It is possible that the lesser incidence of clinically evident bronchial fistula after extrapleural dissections in contrast to intrapleural pneumonectomies, is due, at least in part, to the greater ease with which one can free the bronchus

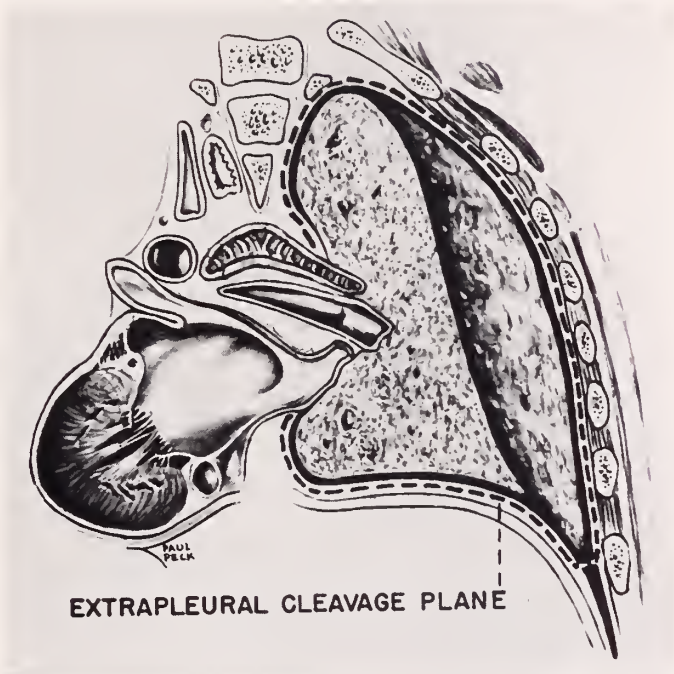


FIG. 3. Sketch illustrating the extrapleural cleavage plane and the frequently small diaphragmatic representation of an empyema.

(By courtesy of the Editors of *Thorax* and the British Medical Association.)

to the carina through the soft clean tissues of the extrapleural approach and so obtain a high amputation. The most important factor in the prevention of post-pneumonectomy bronchopleural fistula seems to be the amputation of the bronchus at the carina and the freeing of the carina from the surrounding hilar and peripleural fascia so that the bronchial stump may retract into the mediastinum and be covered promptly by the adjacent tissues.

Extrapleural resection is applicable to non-tuberculous disease. Many surgeons have mentioned, in their reports, the freeing of very adherent portions of the lung by limited extrapleural dissection as a matter of convenience at the moment. However, it has not generally been recognized that this should be the procedure



of choice. When the extrapleural procedure is planned and developed primarily, tedious and often dangerous intrapleural dissections of adherent lungs are avoided. Since, as already mentioned, the mediastinal aspect of the lung and the mediastinal pleura are usually relatively uninvolved in extensive inflammatory processes of the lung and costal and diaphragmatic pleura, it is usually possible to approach the hilus extrapleurally with ease even in cases in which the entire

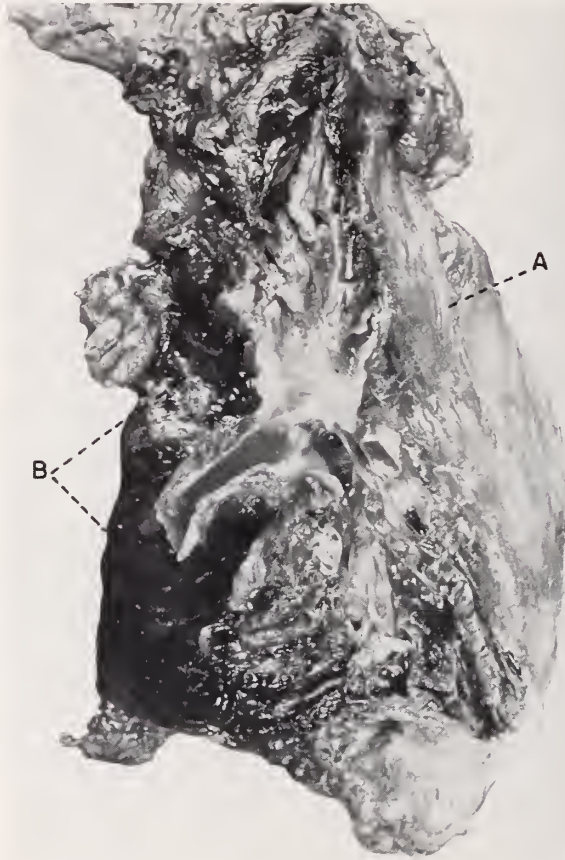


FIG. 4. Lung resected extrapleurally for bronchiectasis, five years after Schede thoracoplasty for chronic empyema. The greatly thickened parietal pleura (A) is in marked contrast to the relatively uninvolved mediastinal pleura about the hilus.

lung is destroyed by chronic abscesses or bronchiectasis. This permits the bronchus to be clamped early in the operative procedure, lessening the danger of bronchial dissemination of infected secretions; after the hilar structures are divided the lung can be freed with less danger of hemorrhage.

#### CASE REPORTS

*Case 1. Total Bronchiectasis, Left Lung; Status Post Extensive Schede Thoracoplasty. History.* P. G., a man aged 56 years, five years previously had developed a left pneu-

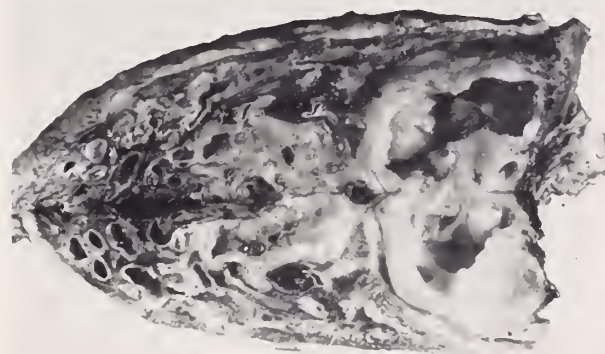


FIG. 5a



FIG. 5b

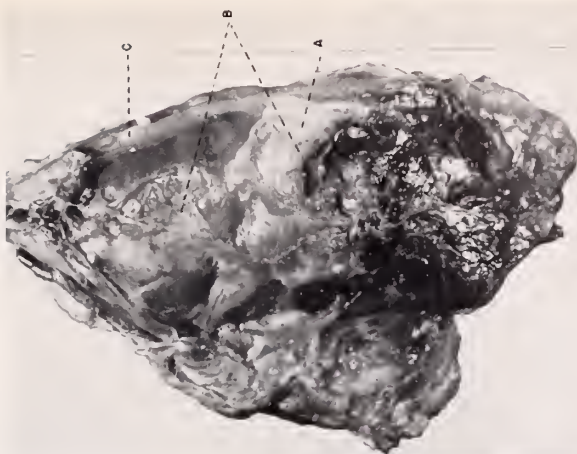


FIG. 5c

FIG. 5a. Cut surface of extrapleurally resected lung destroyed by chronic putrid lung abscess and bronchiectasis.

FIG. 5b. The thick parietal pleura has been removed with the lung.

FIG. 5c. Mediastinal aspect of the same lung showing the bronchus (A), the marked thickened costal and diaphragmatic pleura (C), and the relatively uninvolved mediastinal pleura (B).

monia with subsequent chronic empyema for which an extensive Schede thoracoplasty was done elsewhere. The wound healed but the patient suffered repeated large hemoptyses. Bronchiectasis of the entire left lung was demonstrated. Despite the known dense pleural symphysis, since extrapleural resection was available, pneumonectomy was advised. At operation, despite the marked thickening of the costal pleura, the hilus was approached with relative ease by an extrapleural dissection and the lung and pleura were removed with the skin of the healed Schede wound. The mediastinal pleura was relatively unthickened

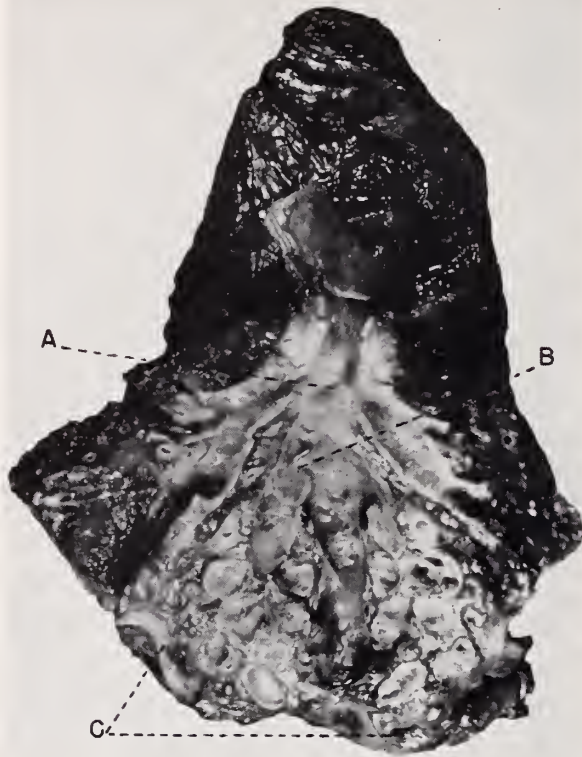


FIG. 6. Lung resected for carcinoma of the bronchus (A), secondary suppurative bronchiectasis (B) and empyema (C). Most of the parietal wall of the empyema, although resected, is not shown.

(fig. 4) and the hilar structures were easy to dissect. The wound healed by primary union and the patient made an uneventful recovery and has remained well.

*Case 2. Chronic Multilocular Putrid Abscess with Bronchiectasis.*

*History.* M. E., a woman aged 50 years, had developed a post-tonsillectomy putrid abscess of the left lower lobe fifteen years previously. In the intervening years she had suffered numerous pneumonic episodes due to spreads throughout the left lung and was a bed-ridden invalid and social outcast, producing large amounts of foul sputum daily. The right lung, fortunately, was uninvolved and her general condition was good. Her physician had previously counseled against resection because of anticipated difficulty with dense pleural adhesions. After observation of other cases of extrapleural resection, he advised extrapleural pneumonectomy.

At operation, despite the marked thickening of the costal pleura, the hilus was easily approached outside the relatively thin mediastinal pleura. The lung and entire pleura



(figs. 5a, 5b, 5c) were removed together and the patient made an uneventful recovery to complete health.

Difficulties in dissection arise not infrequently in the region of the diaphragm since a diseased lung may be exceedingly adherent in this region, especially in the costophrenic sulcus. Policard and Galy (6), and others, have shown that the diaphragmatic pleura differs from the other portions of the parietal pleura in that the deep fibroelastic layer is intimately connected with the muscle of the diaphragm and must be considered part of it. For this reason, a cleavage plane may be difficult to obtain, especially in diseased states. In my experience, a cleavage plane can be developed and the diaphragm identified more easily after

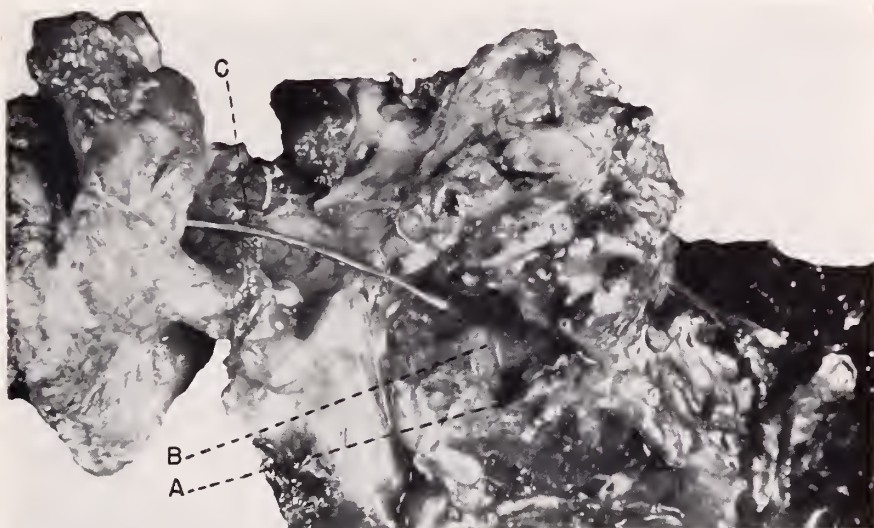


FIG. 7. Right upper lobe containing chronic putrid abscess (B) with bronchial fistula (A). The lobe has been resected extrapleurally with the surgical drainage tract in the chest wall and skin, shown by probe (C).

it has been paralyzed by interruption of the phrenic nerve. Furthermore, the diaphragmatic cleavage plane can always be entered more easily from the mediastinal aspect where there is less pleural involvement, than from the region of the costophrenic sulcus, where the adhesions are often very extensive.

Pulmonary resection is feasible despite the presence of pleural infection or empyema if the procedure is done extrapleurally and the empyema removed with the diseased lung or lobe, as exemplified by the next case.

*Case 3. Carcinoma of the Bronchus with Secondary Pulmonary Suppuration and Empyema.*

*History.* I. F., a man aged 65 years, was found, by radiography and bronchoscopy, to have a carcinoma of the left lower lobe bronchus with atelectasis and suppuration of the left lower lobe. At operation, a basal and subpulmonary empyema was found which was removed with the lung by extrapleural dissection (fig. 6). Penicillin and streptomycin were



administered intrapleurally and intramuscularly following the operation. The patient made an uneventful recovery and no empyema developed.

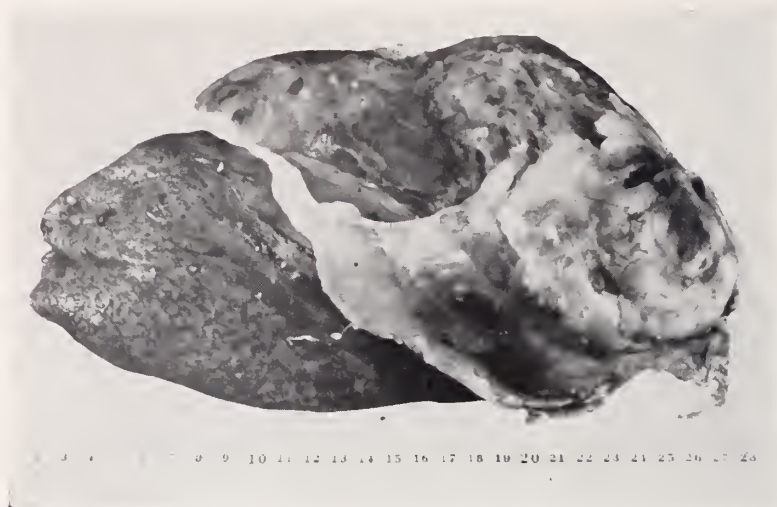


FIG. 8a. The lung containing the "parenchymal" type tumor has been resected with the adherent parietal pleura.

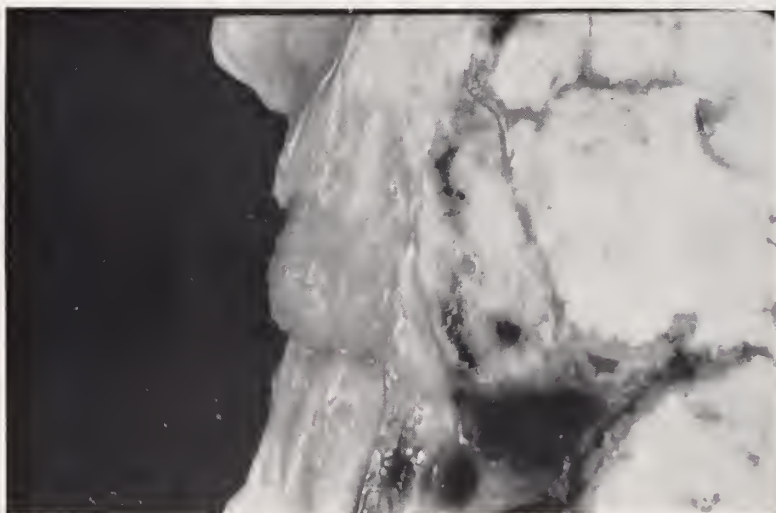


FIG. 8b. The parietal pleura forming part of the pseudo-capsule of the tumor has been resected with the lung.

In cases with chest-wall drainage openings secondary to drained chronic pulmonary abscesses or empyemas, extrapleural dissection facilitates the removal of the pulmonary, pleural and chest-wall disease en bloc.

*Case 4. Chronic Putrid Abscess, Bronchopulmonary-Cutaneous Fistula Secondary to Surgical Drainage.*

*History.* E. F., a man aged 44 years, presented a chronic unilocular putrid abscess of

the posterior segment of the right upper lobe. Pneumonostomy in one stage was performed, for drainage, but the abscess refused to heal. Five months later the right upper lobe containing the abscess and the chest-wall tract with the skin wound were excised en bloc by extrapleural dissection (fig. 7) and the wound closed in layers. The postoperative recovery was uneventful and healing was by primary union.

In cases of bronchiectasis or lung abscess with empyema, in which only a lobectomy is required with the pleurectomy, the interlobar cleavage plane may frequently be entered more easily from the mediastinal aspect of the lung where there is less pleural inflammatory reaction to obscure the fissures.

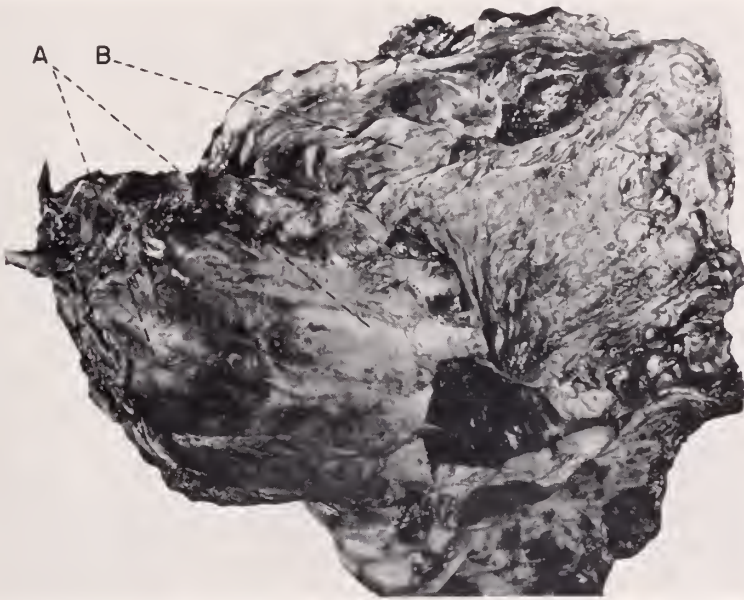


FIG. 9. Segments of five ribs and the intercostal tissues (A), involved by the peripherally invasive type of carcinoma have been resected en bloc with the parietal pleura (B) and the lung.

Circumscribed carcinomas of the lung may be of the "parenchymal" type entirely within the spongy tissue of the lung, or of the "peripheral invasive" type which may actively invade the adjacent chest wall, diaphragm or mediastinal structures (5). The former type usually has a pseudo-capsule about it, is not invasive locally and usually metastasizes to regional lymph nodes to but a limited degree and late in its course. Such a tumor may be resected conveniently with overlying adherent pleura (figs. 8a, 8b). When a circumscribed carcinoma of the peripherally invasive type involves parietes which are resectable, the involved chest wall and adherent and adjacent pleura must be resected en bloc with the neoplasm (fig. 9).

During the surgical exploration of a case of carcinoma of the lung, if the lung is found to be densely adherent to the parietal pleura, the mediastinum and the hilar structures may be exposed much more rapidly and easily by an extrapleural

dissection than by attempting to separate the lung from the parietal pleura. The morbidity and possibly the mortality from exploration in cases of carcinoma of the lung may be reduced by such a technique.

Involvement of the pleura by metastases from an underlying pulmonary carcinoma occurs frequently and the presence of a pleural effusion containing carcinoma cells is at present considered a contraindication to resection. Recently I attempted to remove both lung and pleura in two such cases, but after freeing the pleura and lung from the chest wall and diaphragm by an extrapleural dissection, I found in each case that extensive hilar infiltration prevented pleuropneumonectomy. Nevertheless, the technique of extrapleural dissection may make it possible to operate successfully in a similar, but more favorable, case in the future and the presence of pleural metastases may not in itself prove to be a contraindication to extrapleural pneumonectomy and total pleurectomy.

#### SUMMARY

In cases of combined pleural and pulmonary involvement, it is not adequate to deal with one to the exclusion of the other. The technique of extrapleural dissection makes it possible for both components to be treated simultaneously and permits the fulfillment of the surgical principle of complete excision of the disease, in many types of cases in which it was previously not possible to accomplish this desirable effect. Not only is resection facilitated but complications are minimized. This has been clearly shown in tuberculosis as well as in non-tuberculous disease.

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## THE MIDDLE LOBE SYNDROME

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The clinical entity described by Graham and his associates, and to which they have given the name of "middle lobe syndrome", may be said to have its origin in what was described a generation ago as epituberculosis. Some thirty years ago Eliasberg and Neuland (1) coined the term epituberculosis for a clinical syndrome encountered in children. The outstanding features were a low grade fever and a chronic cough. The sputum did not contain tubercle bacilli but the Mantoux test was positive. X-ray studies showed a sharply defined shadow of a lobe or part of a lobe, and at times retraction of the chest was noted on the same side. The pulmonary shadow would gradually disappear with the patient making a full recovery. They assumed that the condition was a non-specific pneumonia in a tuberculous individual.

Prosoroff (2) described a similar condition and suggested that the lesion consisted of a collapsed lobe produced by the pressure of an enlarged lymph node upon the bronchus, resulting in obstruction and atelectasis. Morelock and Scott Pinchin (3) recorded the findings of a typical case of so called epituberculosis in a 14 year old boy. This patient had the usual sharply defined pulmonary shadow in the right upper lung field and on bronchoscopic examination revealed a "tumor" in the right main bronchus extending into the lumen of the right upper lobe bronchus. Biopsied tissue was found to be covered with normal mucosa, containing black pigment, tuberculous granulations and lymphatic tissue. In an x-ray film taken 4 days later, the pulmonary shadow was no longer present and the affected portion of the lung had reexpanded and had become aerated. In another two weeks occlusion of the bronchus recurred with the reappearance of the original pulmonary shadow. Three weeks later the shadow again disappeared and the patient remained clinically well.

These authors conclude that "epituberculosis is not a clinical or pathological entity but is only a manifestation of enlargement of the root glands which may in certain cases cause pressure, bronchial obstruction and atelectasis". Broek (4) reported a series of 8 cases in which he offered anatomical evidence of the pressure produced by enlarged tuberculous mediastinal lymph nodes upon the adjacent bronchi that caused obstruction of the lumen and atelectasis of the corresponding lung segment.

Zdansky (5) called attention to the frequency with which stenosis of the middle lobe bronchus occurs as a result of the enlargement of the neighboring lymph nodes. This stenosis in turn is followed by atelectasis, retention of secretion and pneumonitis. He also stressed clinical features not infrequently exhibited by these cases affected by a transient febrile, gripe-like disease, associated with a transient shadow of the middle lobe *smaller* in size than the normal middle lobe. At times there is also seen the shadow of an enlarged lymph node at the site of the middle lobe bronchus, thus demonstrating the etiological relationship



of the enlarged node to the transient middle lobe atelectasis as a result of the pressure stenosis. In other instances, and it is to these that the author calls special attention, the picture is not a transient one, but is stationary and chronic. He reports 2 cases.

The *first case* was that of a woman aged 37 years, who suffered from a chronic cough. At irregular intervals, she would develop an acute exacerbation with high fever and profuse expectoration—often blood stained. X-ray examination showed a shadow of the middle lobe with a slight shift of the mediastinum to the right on inspiration. The shadow of a calcified



FIG. 1. Postero-anterior Roentgenogram showing shadow of atelectatic middle lobe

lymph node could also be seen at the site of the middle lobe bronchus. On the basis of these findings, the author diagnosed a stenosis of the middle lobe bronchus with atelectasis, retention of secretion and pneumonitis. Bronchoscopy showed the lumen to be completely obstructed by intensely red mucosa. The clinical picture remained unchanged for a number of years, until one day, after an acute exacerbation, the patient expectorated a calcified broncholith the size of a cherry. An x-ray examination at this time showed the same shadow of the atelectatic lung, but the shadow of the calcified lymph node had disappeared. Within the atelectatic lung, the cylindrical form of bronchiectasis could be seen. It was quite clear that the patient had expectorated the calcified lymph node which was responsible for the stenosis of the middle lobe bronchus but that the indurative and fibrotic changes that had taken place in the middle lobe had led to a permanent shrinking of the lobe.

In the *second case*, a man aged 72 years with emphysema, was dyspneic, cyanotic and febrile. An x-ray examination showed emphysema, bilateral apical infiltration and a shadow

of a shrunken middle lobe. A negative sputum and the absence of caseation and cavitation suggested the diagnosis of bronchus tumor. A bronchogram showed compression of the middle lobe bronchus by a soft mass about the size of a cherry. There was some uncertainty as to whether this picture was that of a bronchial tumor or of a chronic deforming bronchitis with enlarged lymph nodes. The patient's condition declined, he became cachectic and died three months later, having had a profuse hemoptysis several days prior to his death. An autopsy disclosed stenosis of the middle lobe bronchus resulting from pressure of an enlarged lymph node that had penetrated the bronchus at one end and at the other had broken into a branch of the pulmonary artery.



FIG. 2. Lateral Roentgenogram showing shadow of atelectatic middle lobe

The author claims that this type of case is not rare and is due to the fact that the middle lobe constitutes a point of lowered resistance. In children, he writes, it is quite common to find enlarged tuberculous glands causing atelectasis of the lung by pressure upon the adjacent easily compressible bronchi. In the adult this factor, pressure by tuberculous glands is rare. Enlarged inflammatory glands or much more frequently nodes with metastases are responsible for this type of compression and atelectasis. The frequency with which the middle lobe bronchus is involved is explained by the author on the following anatomical grounds: this bronchus is much narrower than the other bronchi, and it comes off the intermediate bronchus at an acute angle. These two characteristics make the middle

lobe bronchus easier to compress by the surrounding enlarged lymph nodes and thus the middle lobe constitutes a point of lowered resistance.

Graham, Burford and Mayer (6) reported 12 cases of a non-tuberculous nature in which middle lobe atelectasis occurred as a result of pressure by enlarged lymph nodes upon the middle lobe bronchus. They too found the same clinical constellation of signs and symptoms, consisting of cough, expectoration, and pneumonitis, associated in the active cases with x-ray evidence of atelectasis of the middle lobe. They treated their cases by lobectomy. At operation they found

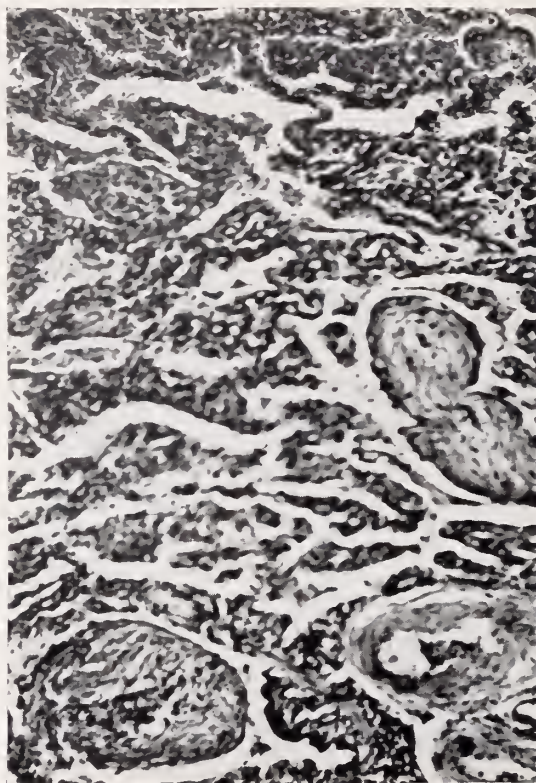


FIG. 3. Photomicrograph of lung tissue showing inflammation and atelectasis

a small, atelectatic middle lobe with compression of the proximal portion of the bronchus by enlarged and firm lymph nodes. The pathological examination showed atelectasis with varying degrees of fibrosis and bronchiectasis. In some instances, small abscesses were found. The nodes were large and hard and showed a non-specific inflammation. The authors believe that any inflammatory process that leads to hilar adenopathy may be followed by bronchial compression, bronchial stenosis and atelectasis. The obstruction in turn leads to pneumonitis, followed by lymphadenitis, thus producing a vicious cycle. They also feel that the bronchial stenosis in some cases may be due at least in part, to infection of the bronchial wall proper with subsequent edema and even stricture formation.

All of their patients were operated upon, had an uneventful postoperative course and remained well. Since the presentation of their findings, the "middle lobe syndrome" has become more readily recognized and as they have demonstrated the safety and the curability of this lesion by lobectomy, this method of treatment has become the accepted form of therapy.

Recently Paulson and Shaw (7) have reported a series of 32 cases of middle lobe atelectasis with only 1 surgical death in 29 lobectomies. Patients, in whom the affliction is less acute and more in the nature of a debilitating disease especially when the expectoration is accompanied by hemoptysis, present greater diagnostic difficulties. Surgical treatment in such instances, in so far as the extent of pulmonary resection is concerned, may have to be decided by the actual operative findings and if necessary by frozen section examination. Such a case was observed at the New York City Hospital and serves as the subject of this report.

#### CASE REPORT

*History.* Mrs. B. C. aged 38 years (case #5651) was admitted to the New York City Hospital on May 14, 1949, from the service of Dr. Milton B. Rosenblatt. There a tentative diagnosis was made of carcinoma of the middle lobe bronchus. She has had a productive cough for the previous two years, and whenever she "caught cold" her cough would become intensified and at times would be accompanied by some hemoptysis. For months she was hoarse. Two months before admission she had a severe attack of cough accompanied by high fever. She was treated for pneumonia and apparently had made a full recovery. For 2 weeks she noticed that she was short of breath. Four days before entering the hospital, she again had a severe attack of coughing accompanied by a hemoptysis of  $\frac{1}{2}$  ounce of blood. She continued to bring up blood. Her appetite became poor and she felt weak and was listless. During the last 8 hours, she has developed pain on inspiration in the right lower quadrant of the chest anteriorly.

*Examination.* The patient was poorly nourished and considerably underweight. She appeared to be in some distress because of chest pain. There was a noticeable hoarseness. Respiratory excursions of the chest were poor throughout. Palpation, percussion and auscultation revealed no abnormalities.

Roentgenogram taken May 16, 1949 showed a dense opacity of the anterior region of the right middle lobe with depression of the short fissure. Atelectasis of this segment of the lobe was diagnosed by Dr. A. L. Bachman. Attempts at bronchoscopy were unsuccessful. On May 24th, a bronchogram was obtained. The middle lobe branches were visualized. The axillary division was found to be normal. The anterior division showed multiple irregular filling defects scattered throughout the proximal 2 inches. There was little visualization of distal branches and no peribronchial alveolar filling of anterior division branches. These findings were thought to indicate a localized atelectasis of the middle lobe, and the changes were considered to be more suggestive of inflammatory disease than of neoplasm although the latter could not be excluded. Repeated examinations of the sputa for malignant cells were negative.

*Operation.* On June 1, 1949, the patient was put under anesthesia with pentothal followed by cyclopropane. When she was fully under, the anesthetist attempted direct intubation. The larynx was visualized and the vocal cords could be seen in normal position. The anesthetist could not introduce the ordinary size intra-tracheal tube and attempted intubation with smaller tubes, finally employing a #26 without success. The patient was returned to the ward. On the following day, she was examined by Dr. O. Risch, the attending laryngologist. A circular constriction below the glottis was found and a biopsy specimen was obtained. This tissue was subsequently reported as "chronic inflammation".



One June 9, 1949, a tracheotomy was performed (by Dr. Seelig) and an intratracheal anesthesia was administered through the tracheal opening. A right postero-lateral incision was then made. The 4th rib was excised subperiosteally. When the chest cavity was entered and the lung exposed, the middle lobe showed a triangular wedge shaped area dark blue in color involving the anterior portion of the lobe. It was quite hard to the touch. The fissure between the upper and middle lobes was developed and the vascular structures were dissected free. However, because of the marked induration, which in parts was almost cartilaginous in character, it was necessary to complete the dissection in a retrograde manner. The middle lobe was now removed *in toto*. The upper and lower lobes were tested by increasing the intrapulmonary pressure. They dilated fully and there was no air leak either from the lung or from the severed middle lobe bronchus. The incision in the chest wall was now closed in anatomical layers and before final closure was made, a mushroom catheter was introduced into the pleural cavity through a stab wound in the 9th intercostal space posteriorly for under water drainage.

The *post operative course* was uneventful and the patient was discharged July 19, 1949. The pathological report by Dr. J. R. Lisa read as follows: "Right middle lobe—The lobe measures 14-6-2 cm. The pleural surface is smooth and has one slightly depressed firm area. The entire lobe is atelectatic, firm and chiefly non crepitant. The bronchi appear normal. On the cut surface there are many small raised, grey firm nodules. Microscopic findings. The common factor in all areas is the atelectasis. Groups of alveoli contain either fresh blood, nests of hemosiderin-bearing phagocytes or organized fibrous tissue containing hemosiderin. The groups are either contiguous or separate. Several parts of the lung are free of these changes. In the region of fresh hemorrhage, the alveolar walls are normal. In the regions where hemosiderin-bearing phagocytes are found, the walls are thickened by histiocytic cells. In the areas of organization the walls are very thick, cellular and fibrous, and enclose small capillaries in the centers."

#### SUMMARY

A case of middle lobe syndrome, so termed by Graham, Burford and Mayer is described. The clinical features of this syndrome, its underlying pathological and physiological causes as well as surgical treatment are discussed.

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## NOTES ON SUBPHRENIC ABSCESS\*

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Of the localized infections, subphrenic abscess is one of the most serious. The mortality is considerable, and in the patients who recover, the postoperative course is generally very much prolonged and too frequently punctuated by complications and recurrent fever referable to incompletely drained foci requiring repeated operations. The use of chemotherapy and antibiotics in recent years has diminished the number of cases of subphrenic abscess, but the mortality generally still remains high and the course after drainage, prolonged. More often than not, the patient with a subphrenic abscess passes through an illness that requires many weeks of hospitalization and leaves him debilitated for a considerable period.

It is true that this is so in many of the cases, because the underlying disease is so often a serious one, either in the nature of a malignant neoplasm, a perforated hollow viscus which leaves a fistula that requires a long time to heal, or an abscess in the liver or elsewhere in the abdomen. The more serious underlying causes occur on the left side, and the left-sided subphrenic abscess, therefore, has always been the most difficult to handle and its prognosis has always been poor.

The problem of subphrenic abscess may be considered from two aspects: first, the underlying disease and second, the abscess itself. It is granted that there will always be a considerable mortality from the underlying lesion, but it seems that prolonged illness, complications and mortality from the abscess itself should be largely avoidable if the condition is recognized early and properly located and drained. It is hoped that the observations made on many patients with subphrenic abscess and the suggestions that follow from these observations, may be helpful in this regard.

One would ordinarily not expect recommendations in this disease to be made by an internist, but because the author developed an interest in surgical problems while on the service of Dr. Berg, and because subphrenic abscess not infrequently appears either to present a problem in the chest or actually involves the chest secondarily, the author takes the liberty at this time to present some of the observations he has made over a period of years. Under the circumstances it is hoped that it will not be considered unseemly for an internist to offer suggestions in the handling of this surgical problem.

No attempt will be made to cover the subject of subphrenic abscess completely. In essence this presentation consists simply of notes which, although arranged under the headings of diagnosis, localization and treatment, occasionally overlap these categories.

Text-book discussions on subphrenic abscess are generally deficient in observations known to many physicians and surgeons. These particularly will be con-

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sidered. In addition, ideas more or less indigenous to this hospital will be presented. Attention will also be paid to certain misconceptions which appear to be prevalent concerning this disease.

#### DIAGNOSIS

The clinical onset of a subphrenic abscess may be extremely insidious even when it is produced by perforation of a viscus. It may produce no symptoms for a considerable period, except for very low grade fever, until it causes secondary involvement of the pleura, or until it actually perforates into the lung or the free peritoneal cavity. The aim should be to recognize the abscess before these complications arise, so that morbidity and the mortality may be diminished. This latent period, during which the abscess is brewing, is prolonged by the administration of antibiotics. Although these drugs have diminished the number of cases of subphrenic abscess, they have also increased the number in which the onset is insidious. Because of the fact that the subphrenic abscess causes so few clinical manifestations in so many cases, it is necessary to rely heavily upon the X-ray examination if the abscess is to be recognized at an early stage. X-ray examination of the diaphragmatic region, including fluoroscopy to determine the mobility of the diaphragm and the presence of a fluid level, should be made in all patients who have unexplained fever in the postoperative period, and in all patients who have unexplained abdominal symptoms and fever even if it is of low grade.

*Fixation of the diaphragm* in an elevated position has long been recognized as diagnostic of a subphrenic abscess in a patient with fever associated with abdominal symptoms or following an abdominal operation. However, it is not recognized widely enough that the diagnosis of subphrenic abscess is practically always wrong if even limited motion of the elevated diaphragm is present, even though there is no other known cause for a postoperative fever. In such cases every other possible cause for the fever must be ruled out before even considering that a subphrenic abscess may be the cause of the elevated diaphragm. Elevation of the right leaf of the diaphragm is not uncommon after cholecystectomy and it may be quite marked, particularly if there is an effusion of bile under the diaphragm or in the subhepatic space; but movement of the diaphragm remains, albeit in a limited fashion, and can be demonstrated with the fluoroscope.

In the case of left-sided subphrenic abscess the diaphragm may not be elevated at all because there is no fixed solid organ, such as the liver, to block the expansion of the abscess downward on this side. If dependence is placed upon the X-ray film in such cases, no indication of a subphrenic abscess may be apparent. Obliteration of the left costophrenic sinus by fibrinous exudate or a small collection of fluid may be attributed to a complication in the lung, and the classical semi-lunar shadow with downward displacement of the stomach bubble or splenic flexure observed in some cases of left-sided subphrenic abscess may not be apparent. Nevertheless, fluoroscopy will disclose fixation of the diaphragm which, together with the clinical manifestations, will make the diagnosis clear.

Elevation of the diaphragm unrelated to the patient's illness, and occurring in a patient who presents symptoms or signs suggesting a subphrenic abscess, may lead to an error in diagnosis. Demonstration of a stomach bubble or of a gas-containing splenic flexure in direct approximation with the diaphragm will obviate this error. It may be advisable, in some cases, to introduce air into the colon or gaseous fluid into the stomach for this purpose. Of course, one would not utilize these procedures if a perforating lesion of these organs is suspected.

On the right side, it is advisable to measure the distance between the dome of the diaphragm and the lower border of the liver to determine whether the entire subphrenic shadow can be accounted for by the liver alone. If this is the case, it is justifiable to conclude that the elevation of the diaphragm is probably due to some other cause than a subphrenic abscess. Here again it may be necessary to outline the colon by air or, in some cases, preferably by radio-opaque material, to demonstrate the lower border of the liver.

An intrapulmonary empyema may be so confined between the lung and the diaphragm as to make differentiation between an empyema and a subphrenic abscess impossible roentgenologically without a pneumoperitoneum. The upper border of the empyema would generally be considered by the roentgenologist to represent the curved, elevated, fixed diaphragm over a subphrenic abscess. And when it occurs on the left side, the lower border which represents the depressed diaphragm, may be considered to represent the crescentric lower border of a subphrenic abscess. Differentiation between the two conditions depends largely on the clinical history. In cases where no cause can be found in the abdomen for a subphrenic abscess, the patient should be questioned carefully in an effort to discover evidence of preceding pulmonary disease that might account for an intrapulmonary empyema. Since intrapulmonary empyemas are most often caused by lung abscess, and since a perforated lung abscess may occur without any pulmonary symptoms, it is important to inquire concerning some incident which might have caused an abscess of the lung. Extraction of one or more teeth, or a period of unconsciousness, even several weeks before the onset of symptoms, may be considered diagnostic of an intrapulmonary empyema if there is no known cause for a subphrenic abscess to account for the shadow in the lower part of the chest.

A *fluid level*, representing a collection of fluid and air in the peritoneum beneath the diaphragm, is pathognomonic of a subphrenic abscess. It should be looked for whenever a subphrenic abscess is suspected, keeping in mind that it is not demonstrable if the X-ray examination is made with the patient lying down and the rays are directed vertically. If it is at all possible, the patient should be fluoroscoped or radiographed sitting up. Should the patient be too ill to be placed upright, he should be examined lying on his side. If the rays are directed horizontally a fluid level is also demonstrable in this position.

In the case of an abscess on the left side there may be difficulty in differentiating between a fluid level in the stomach and one in a subphrenic abscess. Examination during or after the ingestion of barium may prove misleading since the barium tends to collect beneath the level of the fluid in the stomach, and this may



wrongly be considered to represent a gas-containing abscess. An increase in the size of the air pocket following the administration of charged water of a seidlitz powder will demonstrate that the collection of fluid and air is situated within the stomach, but as has been stated, this procedure should not be used when a perforation of the stomach or duodenum or a leak in a gastric suture line is suspected as the cause of the subphrenic abscess. In such cases the administration of a capsule containing either barium or iodized oil together with a small amount of air, at the time of the radiological examination, will help to determine whether the fluid level is caused by fluid and air within the stomach. In this instance the capsule will be seen to float on the surface of the fluid. It is also possible to determine whether the fluid level is situated in the stomach by re-examining the patient after the withdrawal of fluid and air through a Levin tube.

It is often stated that the gas in a subphrenic abscess may be formed by anaerobic bacteria. However, I have not as yet seen a case of subphrenic gas abscess that did not communicate with a hollow viscus. Dr. Ross Golden has demonstrated a case of subphrenic gas abscess that was due to the perforation of a liver abscess which also was gas-containing. In this case it is probable that air entered the liver abscess and the subphrenic abscess from the intestines through the hepatic ducts. For practical purposes one must assume that the presence of gas in a subphrenic abscess indicates that it is caused by perforation of a hollow viscus. Although certain anaerobic bacteria undoubtedly produce gas, it is to be assumed that this gas is absorbed as it is being formed.

A *sympathetic effusion* in the pleural cavity often obscures the diaphragm and may make the diagnosis of a subphrenic abscess very difficult. But where a subphrenic abscess is suspected, the presence of an underlying, clear pleural effusion helps to confirm the diagnosis. The observed sympathetic effusion is free and limpid and may be shifted away from the diaphragm by proper positioning of the patient at the time of the X-ray examination. This may disclose the elevated diaphragm quite clearly and establish the diagnosis of subphrenic abscess. For this purpose the patient should be placed on the side opposite the effusion and the rays directed horizontally, using the vertical fluoroscope.

Too often a pleural effusion following an abdominal operation is considered to be secondary to a postoperative pneumonia when it is really caused by a subphrenic abscess. Postoperative pneumonia rarely causes a pleural effusion. If this is kept in mind, together with the fact that the patient with a postoperative pneumonia practically always has a purulent bronchitis, associated with the production of sputum, this error will be made rarely.

Aside from subphrenic abscess, the condition that merits special consideration as cause for a pleural effusion occurring after an abdominal operation, is pulmonary infarction. The presence of blood in the fluid or the occurrence of hemoptysis are indicative of infarction as the cause. The legs should be examined very carefully for evidence of phlebitis. Not only should the lower extremities be palpated for tenderness and swelling, but the calves should actually be measured. A difference in the size of the calves must be considered to be due to a

phlebitis even though the legs had not been measured before the operation, for a difference in size of the calves is most unusual in persons who have no obvious cause for such asymmetry. Reliance cannot be placed on measurements made with tape of ordinary width, because there is a wide margin of error in measurements made in this manner. It is necessary to use either a tape or strip of paper 2 or more inches in width to make a proper measurement of the size of the calves. Any difference amounting to more than  $\frac{1}{4}$  inch in the size of the calves as measured in this way, is significant.

A postoperative lung abscess may produce a sympathetic effusion, particularly if it is perforated, and this may possibly lead to an erroneous diagnosis of a subphrenic abscess. However, there will almost always be expectoration of some sputum, often foul, to indicate that the patient has an abscess of the lung. Furthermore, the pulmonary lesion will usually be discovered before it is clouded by the effusion if, as is usually the case, an X-ray examination of the chest is made during the first week or two of fever after the operation.

The diagnosis of subphrenic abscess is most difficult when a sympathetic effusion obscures the diaphragm in a patient who has had no obvious cause for a subphrenic abscess. In such cases the pleurisy is often considered to be either tuberculous or cancerous. Among other conditions, one must consider diverticulitis, perforating intestinal foreign bodies, an abscess of the superior pole of the kidney, an abscess of the tail of the pancreas and amoebic abscess of the liver. Practically always, in these patients in whom the presenting signs may be referable to the complicating pleural effusion, a careful history will disclose some abdominal symptoms, preceding the present illness perhaps by many months, but which when carefully considered, lead to further investigation that discloses the abdominal cause for the pleural effusion.

A sympathetic effusion together with fixation of the diaphragm may occur in a subphrenic hematoma. This occurs not infrequently following splenectomy for purpura hemorrhagica. The hematoma need not be infected to produce a sympathetic effusion in the adjacent pleural cavity. It is therefore justifiable, in such cases, to observe the patient for a considerable period before considering seriously the possibility of an abscess under the diaphragm.

*Empyema:* The difficulty in differentiating between an infrapulmonary empyema and a subphrenic abscess has been mentioned and the importance of the clinical history in the differentiation of these conditions has been stressed. The error of considering a subphrenic abscess as an empyema may be made not only roentgenologically but also after aspiration of the chest. One may wrongly fail to consider the possibility of a subphrenic abscess when pus is obtained by aspiration at a rather high level, such as the 7th or 8th intercostal space. The fact that the needle has entered an abscess which is entirely beneath the diaphragm, even though the aspiration has been made so high, may be recognized only at operation when the pleural cavity is entered and is found to be entirely clear. The possibility that one is entering a subphrenic abscess and not an empyema should be born in mind if it is necessary to insert the aspirating needle deeply in order to obtain the pus. This error will usually be obviated if deep aspirations

for empyemas are avoided. It is our experience that they are unnecessary even in the case of interlobar empyemas if proper localization is made during the preliminary X-ray studies.

In previous years, the clear sympathetic effusion over a subphrenic abscess usually became infected and produced an empyema if the subphrenic space was not drained, while today, with the use of chemotherapy and antibiotics, such effusions frequently remain clear or, in fact, disappear, disclosing the elevation of the diaphragm by the underlying abscess. However, there still occur cases in which subphrenic abscess is not recognized until it becomes complicated by an empyema. The surgeon will not be caught unawares if the possibility of a subphrenic abscess is born in mind in all empyemas in which there is not clear evidence of an etiology in the lung. In such cases, particular attention should be paid to abdominal symptoms which the patient may tend to minimize, and a thorough examination be made from the standpoint of a possible subphrenic abscess. When draining a basal empyema in these cases, the diaphragm should be carefully inspected and palpated. Adherent exudate should be removed in a search for a tract through the diaphragm and if there is any unusual bulge or localized area of induration or softening in this region, it should be aspirated. These maneuvers disclosed a subphrenic abscess in one of our patients in whom a history of renal colic several years previously had not been investigated, and she was operated upon for what was considered to be simply an empyema. Further investigation revealed a stag-horn calculus and a pyonephrosis that had caused the unsuspected subphrenic abscess.

In this connection it should be pointed out that an empyema does not perforate through the diaphragm. In the case of an empyema together with an adjacent subphrenic abscess, the subphrenic abscess should be considered as the cause of the empyema. It is necessary to bear this in mind so that the cause of the subphrenic abscess in the abdomen may be searched for and found. A false assumption that the subphrenic abscess is secondary to the empyema would lead to complacency on the part of the surgeon and neglect of the lesion underlying the subphrenic abscess which might require special attention if the patient is to be cured.

There are occasional cases, however, in which a pulmonary abscess causes a subphrenic abscess. But even if the abscess in the lung is situated adjacent to the diaphragm, the subphrenic abscess does not occur by perforation of the pulmonary lesion through the diaphragm. Attention is called to a case of staphylococcus empyema which had perforated peripleurally to reach the subphrenic region by skirting the outer border of the diaphragm (1). In other cases, the subphrenic abscess occurs, not by direct extension of the infection, but by a roundabout route. Bacteria, entering the greater circulation by way of a pulmonary vein adjacent to the wall of the abscess in the lung, cause either a metastatic or embolic abscess of the spleen. The splenic abscess itself may perforate beneath the diaphragm or it may cause a suppurative phlebitis of the splenic vein. This, in turn, produces a pylophlebitis which may lead to the formation of liver abscesses, one of which may perforate beneath the diaphragm.

Examples of both of these sequences have come under our observation, and, although rare, they must be considered in patients who have a lung abscess with signs or symptoms relating to the upper abdomen, repeated chills, jaundice or an enlarged spleen (2). When a left-sided subphrenic abscess originates from a metastatic abscess in the spleen a splenectomy is advisable to prevent extension of infection to the liver via the splenic vein. It should be borne in mind, however, that a left-sided subphrenic abscess may also be caused by the perforation of an abscess in the left lobe of the liver secondary to the splenic and portal phlebitis. Therefore, it is necessary to search carefully at operation for a perforated abscess in this lobe of the liver before attributing the subphrenic abscess to infection of the spleen.

The expectoration of a large quantity of pus by a patient with a history of fever of unknown origin suggests the sudden drainage into the bronchi of an abscess of the lung. But, as is well known, this may also occur following the perforation of a subphrenic abscess into the lung. In these cases the X-ray films may be very difficult to interpret. There is usually a diffuse clouding of the lower portion of the chest by either atelectatic or inflamed lung, and not infrequently, the roentgen appearance suggests a pleural effusion. When it is known that the patient has a subphrenic abscess, it is often considered that the perforation is produced by an intervening empyema because of the roentgen appearance. Nevertheless, it may be stated categorically that this is not the case. Empyemas do not perforate through the intact visceral pleura. The subphrenic abscess perforates through adherent lung to drain its pus into the bronchi without an empyema. If there are no adhesions of the lung to the diaphragm over the subphrenic abscess, only an empyema may develop. This empyema may spread between the visceral and parietal pleura, but not into the lung itself. In these cases, therefore, no search should be made for a collection of pus in the pleural cavity.

#### LOCALIZATION OF THE ABSCESS

Our experience with surgical drainage of an abscess of the lung has demonstrated the importance of accurate localization of the lesion to accomplish drainage where it is most superficial. Complete unroofing of the abscess with packing of all its ramifications, can then be accomplished by means of an operation directed to the abscess without traversing normal lung. The remarkable lowering of the mortality of this operation in acute lung abscess, was due to the thoroughness of the drainage as well as the avoidance of complications, made possible by the accuracy with which the lesion was localized. A similar direct approach to a subphrenic abscess where it is most superficial also makes for thoroughness of exposure that is as important here as it is in abscess of the lung. This makes necessary preliminary studies to determine the location of the abscess and the direction in which it is pointing.

A *point of tenderness* is not infrequently present on the chest wall where the abscess is most superficial. This is not only an important diagnostic sign in subphrenic abscess, but also most helpful in determining the place where drain-



age should be carried out. A local fullness of the chest with loss of elasticity of the chest wall, obliteration of the intercostal spaces, and *localized edema* have similar significance from the stand point of diagnosis and localization. This localized area of edema frequently occurs relatively early but is often overlooked because it is not carefully sought for. It not only indicates that the patient with low grade fever of unknown origin has a subphrenic abscess, but is also the best localizing sign short of finding the pus by aspiration or operation.

As in the case of abscess of the lung, it is necessary to study a variety of *X-ray views* to determine the position of the abscess. In all cases, the lateral and both oblique views are required as well as the dorsoventral. Not infrequently, the lateral view shows a localized elevation of only one portion of the diaphragm, and this indicates the relationship of the abscess to the anterior or posterior chest wall. In a subphrenic abscess on the left side, the right anterior oblique view may show the anterolateral portion of the diaphragm to be in its normal position, while the posterolateral portion may be seen to be elevated on the left oblique view, to indicate that the abscess is most superficial in the posterolateral region. Conversely, a normal position of the posterior part of the diaphragm on the left oblique view and an elevation of the anterolateral portion disclosed on the right oblique, indicates that the abscess is situated anteriorly. Utilization of these views will give similar information concerning abscesses situated in the antero or posterolateral regions on the right side. If the diaphragm is obscured by a sympathetic effusion, it is advisable to remove the fluid completely before attempting roentgenographie localization. A localized elevation of the diaphragm may then be disclosed to indicate the position of the abscess.

Accurate localization is easier when there is air in the subphrenic abscess, because the wall of the abscess and the contents of the abscess may then be used as points of reference, rather than a localized diaphragmatic bulge which is only indirectly indicative of the upper border of the lesion. The wall of the abscess outlined by the air within it is better visualized on over-exposed or Bucky films than on films made with ordinary exposure. The downward extent of the lesion can also be determined by shifting the fluid away from its lower border. If there is sufficient air within the abscess, this may be done by placing the patient on his side and directing the rays horizontally (lateral recumbent position). The mesial and lateral walls may be located by making films with the patient lying on either side. The anterior and posterior borders may be observed on lateral views made in the upright position. A forward or a backward tilt may be necessary, or the patient even be made to lie prone or supine while the rays are directed horizontally in order to show the anterior and posterior borders of the abscess, if the amount of air in it is small.

Occasionally, it is advisable to have a marker on the chest wall visible both radiologically and to the surgeon as a point of reference to the abscess. This is best placed in the intercostal muscle and serves to identify the ribs for the surgeon. A method, utilizing the injection of a mixture of iodized oil and methylene blue or lamp black has been in use at this hospital for the localization of lung

abscess and this has also been found useful in preoperative localization of some cases of subphrenic abscess (3).

It may seem that a painstaking procedure, such as has been outlined, may be superfluous; that one can get a good enough idea as to the location of the lesion without resorting to these X-ray maneuvers, and that the abscess can be located more directly by means of aspiration or by exploratory operation. However, probing with a needle is not without its dangers, particularly on the left side where the stomach and the colon may be perforated. Even on the right side, where this danger does not exist, there still remains the danger incident to punctures of the liver and to spread of the infection into the pleural cavity along the track of the needle. When it is known that the patient has a subphrenic abscess, proper preliminary localization obviates the necessity for potentially dangerous pre-operative needling through the chest wall, and also lessens the danger of aspiration during the operation, because the latter procedure may be carried out where the abscess is most superficial.

#### TREATMENT

Needless to say, once a diagnosis of subphrenic abscess has been made, surgical drainage of the abscess is required. The recognition and the treatment of the underlying lesion is beyond the scope of this paper. Of paramount importance is the complete and persistent drainage of the entire abscess including all its ramifications. For one who is an internist, to say that this cannot be accomplished consistently without wide unroofing of the surface of the abscess, so that all its nooks and crannies can be found and packed, may appear presumptuous. Nevertheless, I cannot conceive of any other way in which one can be sure that the entire lesion has been drained or that drainage will continue unimpaired, so that complete healing can take place promptly. Observation of many cases has convinced me that if this is done, prompt recovery from the abscess takes place, that repeated operations for the drainage of residual foci are avoided, and that the mortality from the abscess itself is reduced to a vanishing point. Study of cases that did not do well postoperatively, almost always revealed that the interior of the abscess was not or could not be inspected thoroughly, or that there was an underlying lesion that was beyond control.

I cannot agree with any routine type of exposure of the abscess, to be applied to all cases. The surgical approach must be considered individually in each case, and the determining factor is the location of the lesion for its drainage, as well as the site and disease of its origin. The latter should be considered a separate problem. The location of the drainage should depend upon where the abscess is most superficial. If this is in the upper abdomen, then the approach should be in the upper abdomen where it abuts on the abdominal wall. If it abuts upon the lower ribs, the approach should be through the lower ribs, and if the approach necessitates going through the diaphragm adjacent to these ribs, then the pleural cavity should be closed off or circumvented and the incision carried

out through the diaphragm. Finally, in those cases in which the abscess is more centrally situated, it is necessary to open the chest more widely, and make a pure transdiaphragmatic approach to drainage.

Previous objections to the transthoracic drainage of subphrenic abscess, which have made an indecisive low opening preferable to many surgeons in previous years, no longer hold. The use of antibiotics, improvement in methods of anaesthesia, and the ability to inflate the lung completely as desired, to keep it inflated and to obliterate a pleural dead space by suction or under water drainage, now prevent pleural infections. The application of these newer methods has made it safer to employ a wide exposure through the chest in those cases which are best drained that way, rather than to rely on a subdiaphragmatic incision where such an approach does not yield complete exposure and proper, persistent drainage of the abscess.

Abscesses on the left side are more apt to be multiloculated. This is sometimes due to the intervention of the colon between the loculations. In other cases the spleen makes for the loculation of the abscess. In the latter instance, the problem may be insoluble as long as the spleen is present, and it may be advisable to remove this organ in order to attain a clear view of the topography of the abscess and to pack its tributaries. Secondary thrombosis of the splenic veins may cause infarction of part of this organ. We have observed 2 cases which ran an extremely prolonged course, necessitating repeated revisions and in which bits of splenic tissue were extruded from the wound from time to time. These patients were cured only after the remains of the spleen were finally removed. They would have been spared prolonged illness and many trips to the hospital if the spleen could have been removed initially.

Counterdrainage of infections in the lower abdomen is an accepted surgical procedure. Drainage in more than one place is also employed in the chest. However, counterdrainage does not appear to be frequently employed in subphrenic abscess despite the fact that the surgeon is not always entirely satisfied with his drainage when he operates on a subphrenic abscess. If the objective of the operation, namely, to uncover the abscess, cannot be achieved because the parietal representation of the lesion is small, it seems reasonable that a counter incision be made at some other point where there is also parietal representation.

At some time after the abscess is drained, it is advisable to fill the drained space with radio-opaque gauze. If there is any objection to iodoform packing, plain gauze soaked in iodized oil may be used. Films made in various views will then disclose the extent of the area that has been drained, and comparison can be made with the conclusions reached preoperatively concerning the extent of the original abscess. If the patient still has fever, this study may determine the location of an undrained focus, which may then be found, either by careful inspection or needling through the wound which is still wide open.

When the drainage tract narrows down, iodized oil should be injected into the sinus. The length, shape and direction of the sinus tract will be demonstrated and the presence of a poorly drained neighboring loculation may be recognized. The presence of discrete globules of oil, instead of a stream or patch of

oil continuous with the superficial part of the sinus tract, is caused by the admixture of the oil with exudate and indicates a poorly draining collection of pus which must be evacuated. The injected oil may also demonstrate the presence of a fistula through the diaphragm into a bronchus, or it may disclose a communication indicating an underlying lesion in the stomach, duodenum, colon, gall bladder or liver. The demonstration of such a fistula, is an indication that the drainage tract must be kept open until the fistula in the neighboring organ has either closed spontaneously or is closed by some additional procedure. The information disclosed by the injection of iodized oil before the wound is entirely closed is most useful in preventing recurrence of the abscess and additional dangerous complications.

Although the patient with a subphrenic abscess that has perforated into the lung may be cured by infradiaphragmatic drainage, the results of this approach are generally poor. It is especially important, in these cases, that the drainage through the operation be complete for there is danger of severe infection of the lungs as long as the operative drainage is not thorough and free. Drainage of the subphrenic abscess that has perforated into the lung is required as an urgent procedure. The sudden egress of pus through the bronchi may lead quickly to diffuse gangrenous pneumonia causing the death of the patient, or if he is able to withstand the initial onslaught of the infection, it may cause repeated attacks of suppurative bronchopneumonia followed by bronchiectasis and chronic supuration of the lung requiring lobectomy for its cure. All of this may be prevented if the nature of the process is recognized early and proper drainage of the subphrenic abscess is instituted promptly.

The most certain way of obtaining proper drainage in these cases is by the transthoracic approach to the point of perforation of the lung. Whether this approach should be made anteriorly, laterally or posteriorly may be evident from the roentgen or clinical examination. However, absolutely reliable information may be obtainable by bronchoscopy. After clearing the bronchi by suction, pus may be seen to recur from only one bronchial division. The location of the perforation may be inferred, without fear or error, from the location of the bronchial branch from which the pus repeatedly reappears. In cases of chronic bronchosubdiaphragmatic fistula, lipiodol injected into the sinus tract may delineate the location of the fistula and this may be localized by films made in suitable projections. Where the fistula cannot be demonstrated in this way, a bronchogram made by the instillation of iodized oil through the trachea, may show bronchiectasis localized to only one basal segment and the location of this segment serves for localization of the fistula.

#### SUMMARY

The foregoing notes on subphrenic abscess emphasize certain signs which we have found useful in the diagnosis of this disease. Misconceptions are discussed, and pitfalls in the handling of the cases are pointed out. Reasons are advanced for elasticity in the surgical approach to subphrenic abscess, and methods are outlined for its localization which is necessary for adequate drainage.



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## BILATERAL TRIGEMINAL NEURALGIA

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The treatment of trigeminal neuralgia scarcely falls into the category of a controversial subject. It has been generally accepted that the surgical treatment of this syndrome is the sectioning of the posterior root between the brain stem and the Gasserian ganglion. Whether the approach is through the posterior fossa or *via* the temporal route is of no particular significance *per se*, but it does become a factor when accuracy is essential in selecting the sensory fibers that are to be severed when the symptoms are bilateral.

The sensory branch of the trigeminal nerve (fig. 1) issues from the outer side of the pons, pierces the dura at the petrous portion of the temporal bone and enters the cava Meckelii. The sensory root opens out to form the semilunar Gasserian ganglion. From the ganglion spring three divisions: The ophthalmic, maxillary and mandibular.

The ophthalmic division enters the orbit by way of the sphenoidal fissure where it subdivides and innervates the tear gland and conjunctiva, the nasal mucous membranes, skin of the tip of the nose, eyeball, anterior middle ethmoidal cells, a portion of the sphenoidal sinus, forehead and scalp as far as the vertex.

The maxillary division supplies the upper lip, cheek, side of the nose, lower eyelids and part of the temple, part of the sphenoid and ethmoid cavities, the maxillary antrum, the lower nasal passages, upper jaw, upper teeth and hard palate.

The mandibular branch passes through the foramen ovale, innervates the skin of the cheek, mucosa of the mouth, external auditory meatus, ear drum, skin of the temple and scalp, the anterior two-thirds of the tongue, sub-maxillary and sub-lingual glands and the lower teeth.

The motor branch of the trigeminal nerve passes below and mesial to the Gasserian ganglion through the foramen ovale and innervates the masseter, temporal, pterygoid, tensor tympani, tensor palati, myelohyoid, and the anterior belly of the digastric muscles. The motor functions of the trigeminal nerve is concerned with chewing, protruding, retracting and side to side movements of the lower jaw.

Unilateral trigeminal neuralgia is met with far more frequently than is commonly supposed. Bilateral trigeminal neuralgia, on the other hand, is most unusual and rare.

The etiological factor of pain in trigeminal neuralgia is still unknown. Contributory factors range from infected accessory sinuses and teeth to lowered resistance of the individual patients who have been impaired by exhausting illnesses, such as anemia, infection, and like conditions. Trauma is a possibility. These, however, are only contributory factors, and it must be emphasized that

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the etiological factor is still unknown. It may be stressed, however, that the attitude of the patient and suggestion can definitely modify the pain threshold and the manner of reaction to pain, which varies with the individual patient.

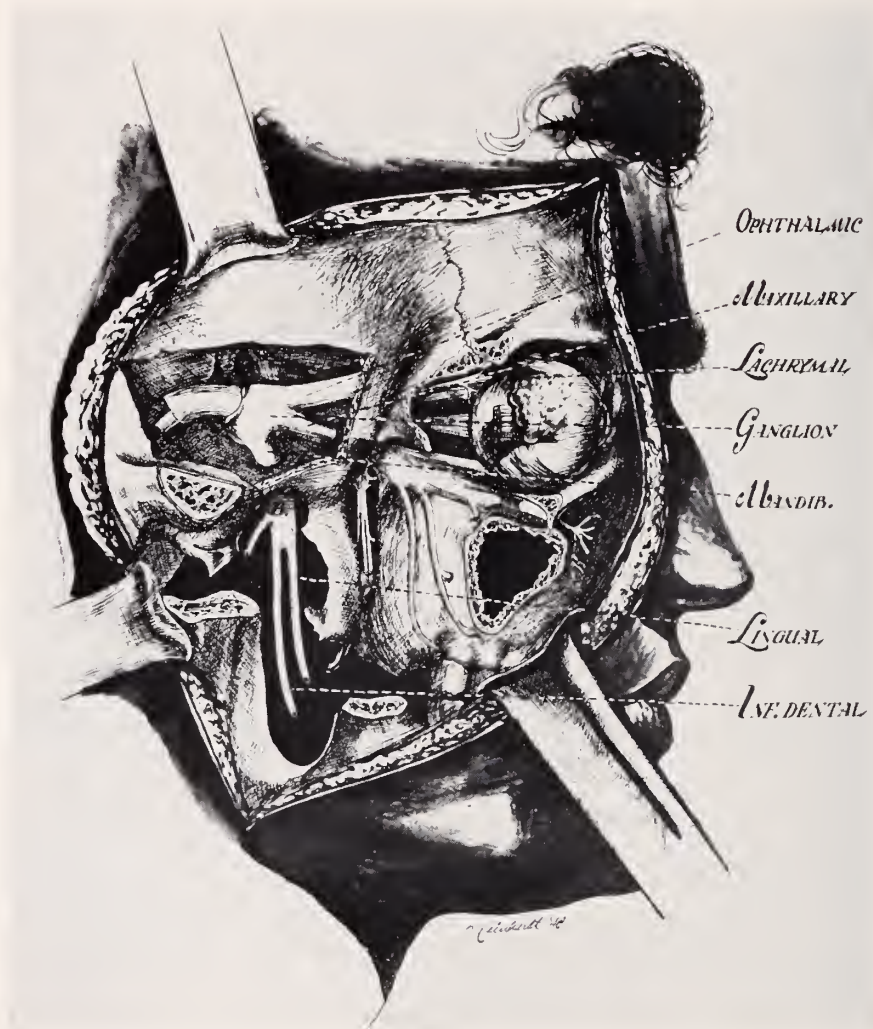


FIG. 1. Motor and sensory fifth. The ophthalmic, maxillary and mandibular branches of the trigeminal nerve in relation to the bony structure and soft parts of face and skull.

This syndrome was known to the ancients. Historical evidence showed that Galen was familiar with this condition. Fothergill, in 1773, gave a very comprehensive description of the syndrome. Little has been added to his clinical description.

The syndrome of trigeminal neuralgia is characterized by paroxysm attacks of lightning-like pain in the distribution of the fifth cranial nerve. It may involve

the ophthalmic branch, the maxillary branch, or the mandibular branch, or any combination of the three. In the author's series ninety-eight per cent of the patients suffering from this syndrome had involvement of either the maxillary or mandibular branch, or both. Pain occurring primarily in the ophthalmic branch accounted for less than two per cent. Pain is usually limited to the anatomical field of the fifth nerve, rarely crossing in the course of the paroxysms, and seldom radiating beyond its limits. The syndrome may undergo long remissions, vanishing completely for months and occasionally for years. With the passage of time the symptoms become more chronic and more severe and appear at most irregular intervals.

In this series, fourteen patients out of more than one thousand had pain involving the trigeminal nerve on both sides. Fourteen patients had areas of excitation along the vermilion border of the lower or upper lip ("trigger zone"), which when stimulated would produce an attack. These "trigger zones" are not essential for the diagnosis. In only two of these patients was there evidence of bilateral involvement at the time of the inception of the syndrome.

Trigeminal neuralgia must be differentiated from other conditions that occur about the oral cavity, head, and face. These are familiar to our readers and hence the problem of differential diagnosis will not be treated in this presentation.

That a diversity of lesions have been found in the Gasserian ganglion in patients with trigeminal neuralgia is not surprising. To date, there is no definite demonstrable pathological lesion in the ganglion or in the nerve to account for these paroxysms of pain. The pain of trigeminal neuralgia is probably the most distressing intractable form of nerve pain. The severity of a major attack cannot be exaggerated.

The treatment of this condition falls into two groups: palliative and surgical treatment. Briefly, under the heading of palliative therapy, chemotherapy, alcohol injection, electrical treatment, and x-ray radiation deserve special mention. Palliative therapy will be limited to alcohol injections. Opinions differ on the relative merits of alcohol injections and surgical operation. Advocates of alcohol injections emphasize that this method of therapy not only establishes a definite diagnosis, but the patient is introduced to the anesthesia of the face which he must accept for the relief of pain.

The disadvantages, however, should be enumerated and stressed. Alcohol injection is an extremely painful procedure and not always successful. The flow of alcohol cannot be controlled. Not infrequently, the solution diffuses up to the Gasserian ganglion, thus anesthetizing the whole area supplied by the trigeminal nerve. The proximity of the sixth cranial nerve to the maxillary branch at the foramen rotundum has been the cause of sixth nerve palsy. Injecting the mandibular branch at the foramen ovale invariably results in paralysis of the motor root, definitely interfering with occlusion of the teeth and the wearing of artificial dentures.

Peripheral avulsions of the various branches is still an accepted method of treatment in some sections of the world. Unfortunately, the period of relief is usually of short duration, because of regeneration of the nerve.



Division of the sensory root for the treatment of trigeminal neuralgia between the Gasserian ganglion and the brain stem is the generally accepted method of surgical treatment of this syndrome. The accurate differential section of the sensory root of the trigeminal nerve immediately posterior to the Gasserian ganglion was introduced by the author in 1934, whereby the ophthalmic branch can be preserved in its entirety and the motor root left untouched. The importance of this procedure, which is applicable in ninety-eight per cent of unilateral trigeminal neuralgia should need no further comment. However, it is worthy of reiteration that the ophthalmic branch can be preserved and the motor root left intact, thereby precluding any eye complications and any interference with the masseter muscles. The dental profession is better able to evaluate the importance of the preservation of the motor root than any other group. Proper occlusion and proper fitting of dentures is definitely influenced by the preservation of the fibers leading to the muscles of mastication.

The value of accurate differential section in unilateral trigeminal neuralgia needs no further emphasis. However, the value of accurate differential section in bilateral trigeminal neuralgia cannot be over-emphasized or unduly stressed. The necessity of preserving the ophthalmic branch in bilateral trigeminal neuralgia is evident. The import of preserving the motor root in a bilateral trigeminal neuralgia is definitely an *essential* without which these patients would be unable to innervate the masseter muscles. The value of the temporal approach in carrying out the accurate differential section is paramount since under actual direct vision the procedure can be done most accurately. The margin of safety between the temporal approach and the posterior fossa is definitely in favor of the temporal approach.

Medullary tractotomy, as introduced by Sjoquist for the relief of pain in trigeminal neuralgia and modified by Weinberger, has its limitations, because of the posterior inferior cerebellar artery and the potential post-operative neurological sequela.

#### SENSORY ROOT SECTION FOR TRIGEMINAL NEURALGIA

The operation is carried out through the temporal approach. The patient is in a sitting position. A simple head rest supports the head (fig. 2). The operation is done under general or local anesthesia. Preliminary medication is optional. An incision  $2\frac{1}{2}$  inches long at right angles to the Zygoma is made in the skin  $\frac{1}{2}$  inch in front of the tragus (fig. 3). The temporal fascia is incised and separated from the muscles. The muscles are incised parallel to the fibers and the squamous portion of the temporal bone is exposed. The skin and muscles are held apart with a self-retaining retractor (fig. 4). An opening is made in the bone with a perforator and burr and enlarged to about the size of a quarter (one inch across) down to the base of the skull. Bleeding from the dura, if any, is controlled with electro-coagulation. The temporal lobe of the brain is then elevated with a lighted retractor placed extradurally, separating the dura from the bone. The foramen spinosum is exposed and the middle meningeal artery is coagulated at this point and cut with a long handled knife. Some surgeons prefer ligating the artery, some plug the foramen spinosum with a wooden plug or use cotton or

bone wax. Elevation of the dura is continued until the foramen ovale, which lies mesial and slightly anterior to the foramen spinosum, comes into view.

By retraction of the temporal dura, the attachment of the temporal dura to the dura propria, the latter a sheath of the ganglion, comes into view. By careful dissection, the temporal dura is separated from the dura propria and fluctuation of the cerebrospinal fluid in the ganglion may be seen. The ganglion is then in-



Fig. 2. Klemme Headrest and position of patient on table (temporal approach)

jected with one per cent novocaine. This not only controls pain, if the operation is done under local anesthesia, but helps to prevent oozing and tends to lessen shock when manipulating the sensory root.

The superficial petrosal nerve is often seen coarsing along a bony groove to the under surface of the ganglion. This can be avoided by careful, sharp dissection. Venous ooze is controlled by electro-coagulation or by small muscle implants. Some surgeons prefer the use of fibrin foam, oxycell, etc.

When the ganglion is exposed so that the three branches anterior to the gan-

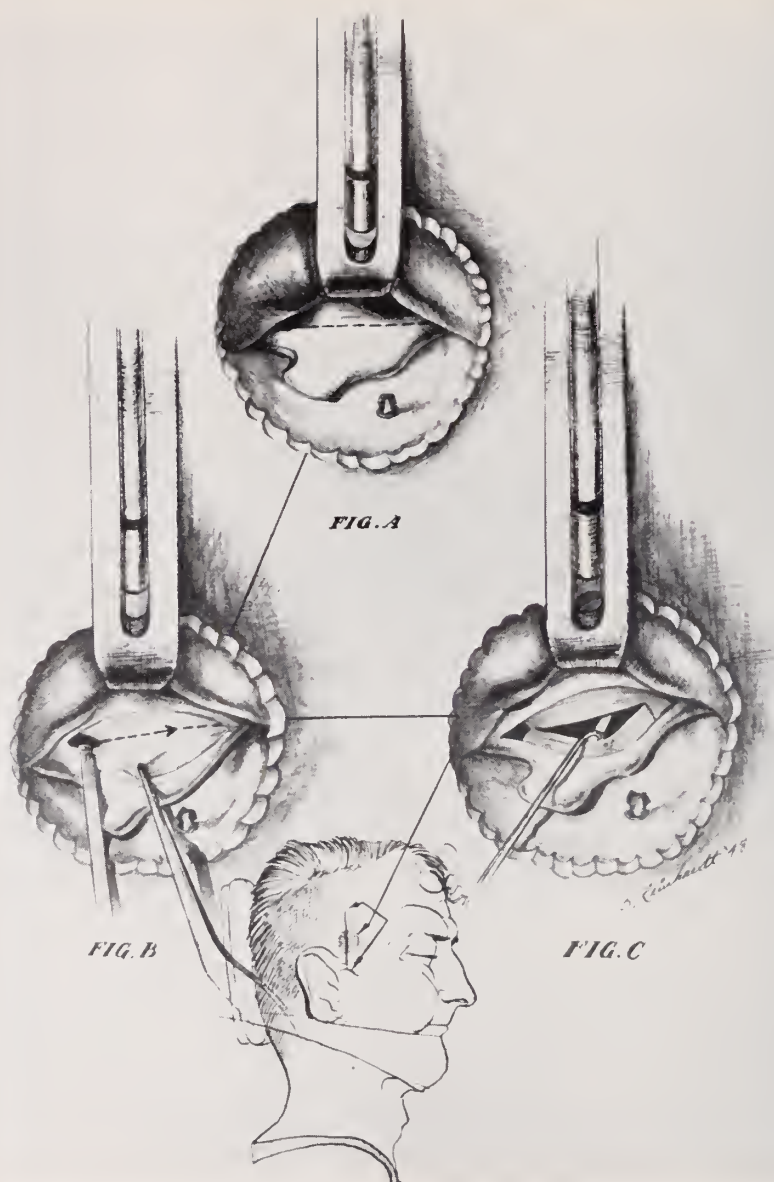


FIG. 3. A. Foramen spinosum and ganglion exposed. B. Direction of spatula through ganglion, separating ophthalmic fibers from maxillary and mandibular branches. C. Sensory fibers cut, motor root intact, ophthalmic branch intact.

gion as well as the posterior root are visualized, the dura propria is incised with a sharp pointed knife from the junction of the ophthalmic and maxillary branches anteriorly across the ganglion to the posterior root (fig. 3). Retracting the dura propria gives a good view of the ganglion and the sensory root. Placing a spatula

between the ophthalmic and maxillary branches anteriorly, the spatula is gently carried posteriorly through the ganglion into the sensory root, thus separating the ophthalmic fibers from the maxillary and mandibular fibers (fig. 3). A hook is then placed around the fibers leading to the maxillary and mandibular branches



FIG. 4. Klemme Self-Retaining Retractor, in place

and these fibers are cut with a knife or scissors. The motor root, lying mesial to the sensory root and running diagonally across the cava Meckelii, is left intact.

When the dura propria is incised a free escape of cerebrospinal fluid occurs. This is removed by suction. Suction is used throughout the operation and is indispensable. Satisfied that all bleeding has been controlled, a small bit of muscle is placed in the cava Meckelii to preclude any ooze flowing into the



posterior fossa. Ringer's solution is then injected subdurally to belly out the dura and bring the dura in contact with the skull. The wound is closed in separate layers using silk for the muscle, fascia, galea, and skin. The average stay in the hospital is five to six days.

Patients stand the operation very well and few complain of paresthesia following the operation. The psychological make-up of the individual patient is a marked determining factor. Of the 14 patients herein reported all were completely relieved of pain on both sides. None had any eye complications and none had any difficulty with artificial dentures or occlusion.

## CASE REPORTS

NO.	NAME	SEX	AGE	FIRST SIDE AFFECTED	DURATION OF PAIN	OPERATION	SECOND SIDE AFFECTED	DURATION OF PAIN	OPERATION	RESULTS
1	L. E.	F.	72	Right	12 years	1939	Left	1 year later	1941	No eye complications. Motor root intact.
2	M. M.	F.	66	Right	5 years	1937	Left	7 years later	1945	No eye complications. Motor root intact.
3	E. H.	F.	62	Right	8 years	1941	Left	2 years later	1944	No eye complications. Motor root intact.
4	K. H.	F.	76	Right	8 years	1936	Left	6 months later	1937	No eye complications. Motor root intact.
5	C. E.	F.	66	Right	8 years	1939	Left	5 months later	1940	No eye complications. Motor root intact.
6	J. D.	M.	65	Right	25 years	1939	Left	6 years later	1940	No eye complications. Motor root intact.
7	E. B.	F.	49	Left	5 years	1942	Right	2 years later	1944	No eye complications. Motor root intact.
8	M. B.	F.	50	Right	10 years	1942	Left	2 years later	1944	No eye complications. Motor root intact.
9	L. A.	F.	84	Right	5 years	1943	Left	2 years later	1945	No eye complications. Motor root intact.
10	R. L.	F.	76	Right	9 years	1939	Left	2 years later	1942	No eye complications. Motor root intact.
11	C. R.	M.	46	Left	6 years	1937	Right	3 years later	1942	No eye complications. Motor root intact.
12	L. T.	M.	81	Right	19 years	1936	Left	3 years later	1939	No eye complications. Motor root intact.
13	J. P.	M.	58	Bilateral	5 years	1945	Left	2 months later	1946	No eye complications. Motor root intact.
14	A. C.	F.	61	Bilateral	5 years	1943	Right	1 month later	1943	No eye complications. Motor root intact.

Only two patients, Nos. 13 and 14, had bilateral symptoms from the beginning of the syndrome. None had any eye complications. None had any interference with masseter power on either side. No interference with the wearing of dentures or occlusion.

## SUMMARY

The value of accurate differential section in unilateral and particularly bilateral trigeminal neuralgia hardly needs any comment. In both unilateral and bilateral trigeminal neuralgia the operative risk is less than one-half of one per cent. The average stay in the hospital is five to six days, post-operatively. Preservation of the ophthalmic branch precludes eye complications; preservation of the motor root precludes interference with occlusion.

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# TUMORS OF THE INTRACRANIAL PORTION OF THE OPTIC NERVE\*

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A paper published by Davis (6) in 1940, on primary tumors of the optic nerve contains a report of five cases and a very thorough review of the literature. He states that about 380 cases have been recorded, some 75 of which he adds to the series assembled by Hudson (7) in 1912, and Lundberg (9) in 1934. In 1944 Burke (1) brought the total number of cases reported to 446. The thesis of Dr. Davis' paper is the relationship of gliomas of the optic nerve to Recklinghausen's disease. This relationship is shown in the five cases reported by him, and in 33 of the cases collected by him. Cushing had 22 cases of optic nerve and chiasmal tumors (5), 7 of these were detailed in a paper published with Martin in 1923 (10). A brief description of two others is given in his paper on "The Chiasmal Syndrome", published in 1930 (4).

In the past 17 years, six patients having primary tumors of the optic nerve have been encountered on the neurosurgical service, among upward of 700 craniotomies for brain tumors.

## CASE REPORTS

*Case 1. (Mt. S. H. #454804) B. G., a 15 year old girl, was blind in the left eye for at least seven years. She had pigmented spots over the body. Both optic nerves were found involved at operation. There has been slow progression over nine years of further observation.*

*History.* In 1940, at the age of 15 years, the patient was admitted to the Mount Sinai Hospital. Some 7 or 8 years prior to that time, it had been noted at school that she was unable to see with the left eye. She was referred to the hospital in 1940 because perimetric studies showed a defect in the temporal field of the right eye.

*Examination.* Aside from very many café au lait spots scattered over the body (fig. 1), the only physical abnormality noted was in the eyes. Both pupils reacted to light directly and consensually. Vision in the right eye was 20/20. In the left eye, there was light perception in the temporal field only. The right eye showed a temporal field defect. There was pallor of the entire left optic disk, and relative pallor of the temporal half of the right disk.

The cerebrospinal fluid pressure was normal, the total protein of the fluid being 43 mg. %. The basal metabolic rate was minus 11%, electroencephalography was non-contributory. The sugar content and the morphology of the blood was normal. The x-ray studies of the skull showed a flat sella; the left sphenoid fissure was narrower than the right. Pneumoencephalography disclosed a lack of filling of the chiasmal cistern.

*Course.* On April 25, 1940, the chiasmal region was explored through a right frontal craniotomy. The right olfactory nerve was found to be thickened. The right optic nerve was estimated at two and a half times the normal size, the left was enlarged about three times the normal. The nerves joined at the chiasm to form a sharp V. Grossly the chiasm did not appear involved. The only tissue removed was the right olfactory nerve. Dr. Globus reported this as follows: "No evidence of true neoplastic formation could be recognized. The olfactory bulb shows in some parts a disruption of the normal cellular pattern, due to some irregular cell condensation, with loss of architectural design. The olfactory nerve shows nothing unusual except for a few distended sinusoids giving the impression of some embryonal residues". She was discharged to receive radiotherapy.

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In 1941 she was readmitted to the hospital because of a generalized convulsion. There was no change in her vision or in the pneumoencephalogram. The electroencephalogram suggested a right temporal lobe focus. In 1942 she had a series of convulsions which brought her under observation. In 1949 the left eye was found to be completely blind. She was able to read fine print with her right eye. At this time, skull x-rays showed a distinct enlargement of the left optic foramen, fig. 2.

*Comment.* Even in the absence of histologic proof, the picture is classical, the onset in early childhood, the associated widespread pigmented spots, and the appearance of the nerves at the operation. In spite of the preservation of useful



FIG. 1. Case 1. Café au lait spots on arms and trunk

vision in the one eye, there has been a slow progression, at least on the left side, as shown by the loss of vision and the enlargement of the left optic foramen in the x-ray film fig. 2. She has been under our observation for nine years, the history of known visual disturbances adds at least another seven years, and maybe longer. In spite of the apparent swelling of the olfactory tract, the bulb failed, on histologic examination, to show evidence of Recklinghausen's disease.

*Case 2.* R. B., (Mt. S. H. #509204) a seven and a half year old girl, had an acute onset of swelling of the eyelid, and blindness in the right eye. A craniotomy and biopsy of the optic nerve was done. There has been no progression over a six year period.

*History.* Three weeks prior to her admission to the Mount Sinai Hospital, a seven and a half year old girl developed swelling and redness of the right upper eyelid. The swelling



gradually subsided over a two weeks period. About ten days prior to admission the child stated that she could not see with the right eye.

*Examination.* On admission she was found to have a temperature of 101.2°F., but otherwise the general physical condition was normal. The right eyelids were slightly oedematous, and the right eye protruded slightly. The exophthalmometer reading was 18, in the left eye it was 15½. Motion upward of the eye was limited, the pupil was fixed, and vision was completely absent. The disk was swollen to 5D. The left eye was normal, the vision was 20/20.

X-ray examination of the skull showed a slight enlargement of the right optic foramen (fig. 3). X-ray examination of the orbit after periorbital air insufflation failed to outline any orbital mass.

*Course.* On August 26, 1943, a frontal craniotomy was done under local anesthesia. The right optic nerve from the foramen to the chiasm was four to five times the normal size. The chiasm appeared to be involved at the junction of the right nerve. The left optic nerve



FIG. 2. Case 1. Enlarged optic foramen

was normal in appearance. A biopsy of the right optic nerve was reported as glioma of the optic nerve.

Beginning seventeen days after the operation, she received x-ray treatments for about six weeks. During this period there was complete subsidence of the papilledema and of the exophthalmos.

In 1949, six and one half years later, she showed optic atrophy on the right with absent vision in that eye. The pupil did not react to light either direct or consensually. The left eye showed no abnormality.

*Comment.* Of interest, but not readily explained, is the acute onset of what appeared to be an acute inflammatory condition associated with fever and oedema of the eyelids. The question arises in this case, as it must in all children, as to the accuracy of the history, especially with reference to the onset of visual loss. In this patient, the loss of vision was said to have been complete within two weeks of the onset of her symptoms.

*Case 3. E. F., (Mt. S. H. #532063), an eight year old girl, had progressive loss of vision of the right eye. By craniotomy, the intracranial portion of the right optic nerve was removed. Subsequently the eye-ball was enucleated.*

*History.* In March 1943, an eight year old colored girl was admitted to the hospital complaining of gradual loss of vision in the right eye. The loss had been progressive. She had been completely blind in the one eye for two weeks. There were no complaints referable to the left eye, and no history suggestive of involvement of the nervous system.

*Examination.* Other than a moderate generalized adenopathy, the only abnormalities noted on examination were limited to the right eye. There was proptosis and an increase in sense of resistance to backward pressure on the eyeball. The pupil was dilated and fixed to light. The lower portion of the disc was occupied by a filmy mass of intertwining large and small blood vessels which extended into the vitreous 5D. The retina was elevated below the

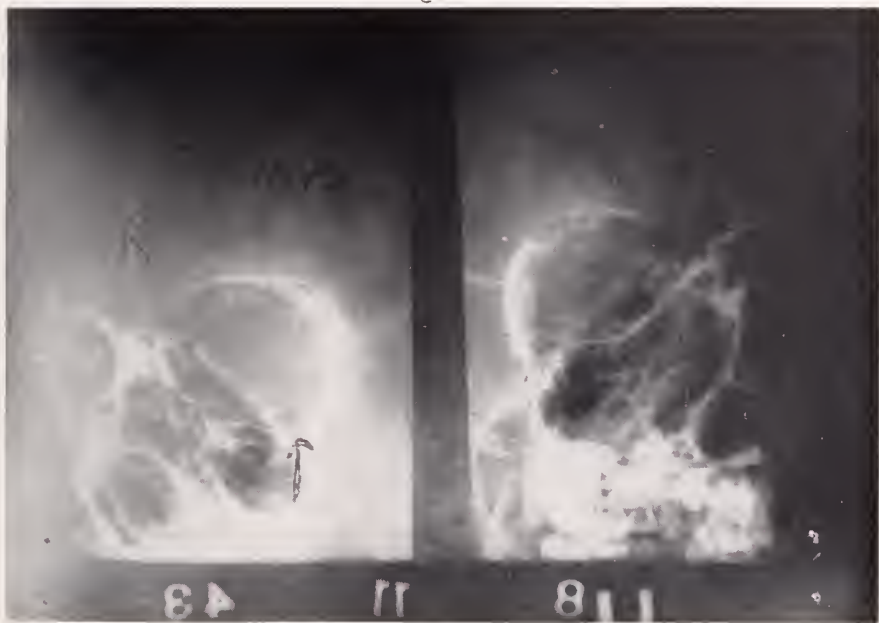


FIG. 3. Case 2. Enlarged optic foramen

disc. All vision was absent in the right eye. In the left eye it was 20/50 with correction. The exophthalmometer reading was OD 22, OS 16. The palpebral fissures measured OD 10, OS 7. The visual field in the left eye was normal. X-ray examination showed the right optic foramen to be twice the size of the left (fig. 4). The electroencephalogram reading was normal.

*Course.* On March 30, 1945, through a right frontal craniotomy, the right optic nerve appeared nodular and about 3 or 4 times the normal size. The enlargement extended from the optic foramen to a point just anterior to the chiasm. The nerve was excised from the chiasm to the optic foramen. The specimen was reported glioma of the optic nerve. A month later the eye-ball and the stump of the nerve were enucleated (Dr. Robert K. Lambert). This was also reported as glioma.

The only follow-up was a report by post card six months after she left the hospital. She claimed to be doing well. Efforts to induce her to return to the city for an examination have been futile.

*Comment.* As in the preceding case, the loss of vision from onset was very rapid, if the history is reliable.

*Case 4. S. G., (Mt. S. H. #536177), a 9 year old girl with a gradual loss of vision over a short period, drowsiness and diabetes insipidus. Visual improvement maintained over a four year observation.*

*History.* Four years prior to her admission to the hospital in 1945 for visual disturbance, this nine year old girl had been in the hospital for a left pyelonephritis. For a year and a half prior to the second admission, there had been increased thirst. For several months she was constantly drowsy, and had fallen behind in her school work. More recently it was noted that her vision was impaired.

*Examination.* The patient was found to be an obese drowsy child who appeared to be chronically ill. Her mental responses were normal. Her blood pressure was 120 systolic and 70 diastolic. The lower pole of the left kidney was palpable. There were no abnormal neurological signs. In both eyes the arteries and veins were tortuous, there was temporal



FIG. 4. *Case 3.* Much enlarged optic foramen

pallor of the left disc. Visual acuity was 10/200 on the right and 20/200 on the left. Visual fields could not be plotted. The fluid intake ranged up to 4900 cc. and the output up to 4600 cc. X-ray films of the skull showed no abnormality, those following the injection of air showed moderate symmetrical dilatation of the ventricles. Electroencephalogram disclosed diffuse disfunction.

*Course.* Exploration of the chiasmal region was carried out by Dr. Benno Schlesinger. The optic nerves at the optic foramina were normal. Beginning about half a centimeter centrally there was an abrupt swelling of both nerves which involved the chiasm as far as it could be visualized.

Following the exploration she received radiotherapy. At the time she left the hospital her vision in the left eye was 20/70 and in the right 20/100. In 1949 the vision remained unchanged. She still had diabetes insipidus. X-ray examination of the skull showed normal optic foramina.

*Comment.* The association of diabetes insipidus with a primary tumor of the optic chiasm is not too frequently observed. Cushing (5) however, noted in his

22 cases of glioma of the optic chiasm that polyuria occurred nine times, and adiposity in eight instances.

In a patient with primary visual loss associated with disturbances of endocrine secretion, or water balance, a tumor of the chiasm must be considered, especially if x-ray examinations of the skull show no abnormality.

All of the patients here reported were females, and four had the onset of the disease in early childhood. In only one case was there evidence of Recklinghausen's disease.

In addition to the four children there have been two adults with primary tumors.

*Case 5.* (Mt. S. H. #393928). *The patient, a 42 year old woman has previously been reported by Learitt (8) as a glioma. Further studies by Dr. Globus have led to a diagnosis of hemangioma of the optic nerves and chiasm. The essential features of the clinical picture are a history of failing vision for at least ten years, beginning in the left eye.*

*Examination.* The left eye was proptosed, amaurotic with fixed pupil and optic atrophy. There was temporal field defect for color in the right eye. The left sphenoidal ridge was eroded and the left optic foramen was enlarged.

*Course.* Exploration was carried out (Dr. Kaplan), the bleeding prevented adequate exploration. The post-mortem examination showed the optic chiasm replaced by a mass of tumor tissue which involved both optic nerves, the tumor on the left extended into the orbit. The microscopic examination revealed a vascular tumor (hemangioma).

*Case 6.* G. G., (Mt. S. H. #595731), a 42 year old woman was readmitted to the hospital 12 years after a craniotomy and biopsy, because of increasing proptosis of the right eye. This had been progressive over 13 years. She died following reoperation.

*History.* A married woman of 42 had first come to the Neurosurgical Service in 1937 because of proptosis of the right eye of a years duration and blurred vision in that eye of six months duration. She had optic atrophy on the right with a poorly reacting pupil. The visual acuity was 3/20 and there was a temporal field defect. The left eye was normal. There were no changes in the x-rays of the skull or optic foramina.

*Course.* Operation disclosed an irregular thickening of the right optic nerve; and on either side of the nerve at the foramen was a small tumor. They looked like small granulations. The larger of the two was removed. It measured 3 mm. in diameter and weighed 30 mg. It was reported a pial meningioma.

She lost all vision on the right but otherwise remained unchanged over the next nine years. Then the proptosis of the right eye began to increase slowly. The x-ray examination of the skull showed thickening of the bones of the right orbit as well as some destruction of the medial part of the sphenoidal ridge (fig. 5).

At the second operation the old frontal bone flap was reelevated. The orbit was unroofed. A cherry sized tumor was seen at the right optic foramen. After its removal and while attempting to remove some remaining shreds a brisk hemorrhage ensued, (it was believed from the internal carotid artery). Although this was controlled the patient died on the twelfth post-operative day. The tumor removed at operation was a pial meningioma. In addition there was an oval tumor 3 x 2 x 2 cm. within the orbit (meningioma), and another meningioma 2 cm. in diameter attached to the oculo-motor nerve was found.

*Comment.* This case resembles, in some respects, case one in the recent report by Craig and Gogela (3). Their patient had 2 meningiomas at the optic foramen and one on the sphenoidal ridge. At the first operation in 1937 on our patient, the 2 small meningiomas were present at the foramen but they were not rec-



ognized as tumors until the report was made of the microscopic study of the one removed. In addition there was involvement of the optic nerve. This latter proved at autopsy 12 years later to involve the chiasm. The intraorbital tumor was probably present at the first operation, and accounted for the exophthalmos noted at that time.



FIG. 5. *Case 6.* Thickening of bones of orbit

#### DISCUSSION

Although primary tumors of the optic nerve are uncommon, there is too great a discrepancy between 2 cases among 388,000 eye patients as reported by Collins and Marshall (2), and Cushing's 22 cases in some 2000 brain tumors. It leads to the impression that the condition is not recognized as frequently as it presents itself. In the absence of confirmatory signs, such as enlarged optic foramina or evidence of Recklinghausen's disease, exploratory craniotomy may be needed to rule out or establish the diagnosis of a tumor of the intracranial portion of the optic nerve or chiasm.

There is also considerable variance in the reported prognosis of the gliomas. On the one hand the statement is made that "most of the patients die within a year after the beginning loss of vision", (11) on the other hand Rea (13) states "Glioma of the optic nerve is benign, its' growth is slow, and is toward the cerebrum". The outcome must be considered from the point of view of vision and of life. Most probably the differences of opinion are due to two factors, the relative little opportunity for personal study of any large number of cases and, as pointed out by Martin and Cushing (10), the probability that the gliomas

may be of different types and variable malignancy. Recently Posner and Horrax (12) reported three verified cases with postoperative follow-up of four and one half, ten and twelve years respectively.

Probably the ideal treatment of tumors of the intracranial portion of the optic nerve would be excision of the involved portion of the nerve. In only one of our cases explored was this possible. Three cases showed involvement of the chiasm, in one, two cases had one nerve and the chiasm involved, while in only one case was a single nerve involved, in which grossly the tumor stopped short of the chiasm.

It is difficult to evaluate what, if any influence radiation therapy has had in arresting the growth of the gliomas, in preserving vision, and in prolonging life. In case two, there was prompt subsidence of both the papilledema and the proptosis, while she was receiving x-ray therapy. In case four, visual acuity improved while under treatment.

The question may well be asked whether in the gliomas operation, other than for the purpose of establishing the diagnosis, is warranted. Those patients whom we could follow and in whom, with or without biopsy, a diagnosis of glioma of the optic nerves was made, have not progressed under observation.

#### SUMMARY

Six cases of tumor of the intracranial portion of the optic nerve have been described. All of the patients were females, and four were children. In our cases the progress of the disease was very slow. X-ray therapy seems to be of value in the gliomas.

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# SPONTANEOUS OCCLUSION OF THE INTERNAL CAROTID ARTERY IN THE NECK

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The sudden onset of muscular weakness or paralysis is commonly the result of cerebral thrombosis, hemorrhage or embolism. In such cases the clinician rarely palpates the carotid arteries in the neck so that spontaneous occlusion of the cervical portion of the internal carotid artery is often overlooked. The clinical picture of spontaneous occlusion of the internal carotid artery in the neck is given little attention in contemporary textbooks.

The common carotid usually bifurcates at the level of the upper border of the thyroid cartilage. According to Lee McGregor (1), should the common carotid bifurcate atypically, the division is always above this level and never below. It is difficult or impossible to differentiate between pulsation of the internal and external carotid arteries by palpation. However, the internal carotid artery is larger than the external so that an absence of pulsation or a marked difference in the carotid pulses above the bifurcation on the two sides should arouse a suspicion that occlusion of the internal carotid artery might exist. Along with the frequent use of cerebral angiography in recent years the carotid arteries are carefully palpated in many patients, and they are exposed surgically whenever angiography is carried out by direct puncture. Thus, cases of occlusion in the carotid vessels which might otherwise escape detection are discovered.

In the following two case reports occlusion of the internal carotid artery in the neck was suspected clinically and proved by surgical exploration:

## CASE REPORTS

*Case 1. History.* A man aged 26 years was admitted to the hospital on October 18, 1946, because of a right hemiplegia and aphasia. He had been in good health until January 1946 when, while on an Army transport returning from overseas, he suddenly became aphasic. A few hours later he developed a right hemiplegia. He slowly improved during a period of several weeks. Shortly before he was admitted to the Mount Sinai Hospital his condition declined. He again became markedly aphasic and the hemiplegia became more pronounced, especially in the right upper extremity.

*Examination.* There was a profound mixed aphasia and a right hemiplegia. The force of the carotid pulsation on the left side above the bifurcation showed a definite diminution. The cerebrospinal fluid was clear and colorless under a pressure of 50 mm. of water. An electroencephalogram disclosed a depression in the amount and voltage of alpha activity on the left side, and a moderate amount of 2.5 per second activity diffusely on the left side.

*Course.* On October 25, 1946 the common carotid artery, the bifurcation and the internal and external arteries were exposed with the use of local anesthesia. The internal carotid artery above the bifurcation was hard and cord-like. Injection of 35 per cent diodrast into the common carotid artery for arteriography showed that only the branches of the external carotid artery were visualized.

*Comment.* This patient had been seen by several physicians and had had a prolonged period of hospital observation shortly after the onset of his disease. Occlusion of the carotid artery was not suspected, and there is no record of the carotid arteries having been palpated prior to his admission to Mount Sinai Hospital. This case demonstrates the value of palpating the carotid pulses in every patient who is suspected of having a vascular disorder of the brain.

*Case 2. History.* A man aged 54 years was admitted to the Mount Sinai Hospital in March of 1950. He had been in good health until January 1, 1949, when he suddenly complained of weakness, and collapsed. He was unconscious for fifteen or twenty minutes. On regaining consciousness he displayed a complete left hemiplegia. He was admitted to another hospital where his blood pressure was found to be 134 systolic and 90 diastolic. A spinal puncture disclosed clear colorless fluid under a pressure of 78 mm. of water; it contained two lymphocytes, and a total protein of 35 mg. per cent. X-ray examination of the



FIG. 1. (Case 2). Longitudinal section of the right internal carotid artery, showing marked arteriosclerotic narrowing with an organizing thrombotic occlusion.

skull showed no abnormalities. He was restless, noisy, confused and incontinent. He slowly improved and was discharged with the diagnosis of "thrombosis of the right middle cerebral artery". The left hemiparesis persisted, although power in the left lower extremity returned sufficiently to enable him to walk. His left upper extremity remained weak and spastic.

He was then admitted to the Mount Sinai Hospital for investigation, because examination disclosed absence of the right carotid pulse above the carotid bifurcation. An electroencephalogram showed a large amount of delta activity with frequencies as low as 1.5 per second, especially in the right frontal, right inferior frontal, right ear lobe, and right inferior parietal electrodes. On April 12, 1950, the right carotid arteries were explored. The common carotid and external carotid arteries appeared relatively uninvolved. The internal carotid artery from the bifurcation and for a distance of about 3 cm. was converted into a solid non-pulsating cord. The thrombosed segment was resected and a common



carotid-jugular vein shunt was made. The patient tolerated these procedures well and convalesced rapidly. Although he thought that there was improvement in the use of his left lower extremity, there was no objective evidence to substantiate his subjective feelings. The electroencephalogram after operation was essentially similar to the one done on admission. The resected artery showed a marked arteriosclerotic narrowing with an organizing thrombotic occlusion (fig. 1).

*Comment.* For more than a year this patient was believed to have had the common variety of cerebral thrombosis. Simple palpation of the carotid arteries in the neck would have led to the correct diagnosis. Whether or not early resection of the thrombosed internal carotid artery would have altered the clinical course in this patient, is, of course, not certain.

#### DISCUSSION

The recognition of occlusion of the carotid arteries in the neck as a cause for the sudden occurrence of hemiplegia makes it necessary for the clinician to palpate the carotid arteries in every patient with a "stroke". Although this syndrome has been known for sometime, it has received scant notice in most neurological texts. Likewise, pathologists are not generally aware of the condition, so that the carotid arteries in the neck are rarely examined even in obscure cases of cerebral vascular disease. A brief perusal of the literature (2, 3) discloses that carotid occlusion in the neck may occur during early adult life. Our first patient was only 26 years old, and occlusion of the internal carotid has been reported in this age period by others. Chao *et al.* (4) reported a man of 27 with occlusion of the left internal carotid in the neck discovered during arteriography. Gurdjian and Webster (5) reported four cases of spontaneous thrombosis of the carotid arteries in the neck. One of their patients was a 24 year old man.

Atherosclerosis is the most common cause of non-traumatic vascular occlusion. It may occur at an early age. Syphilitic arteritis, non-specific arteritis, and embolism may also result in acute vascular occlusion of the carotid vessels in the neck.

In the reported cases of occlusion of the internal carotid artery in the neck there was considerable variation in symptomatology. In some cases the onset was dramatic. In others prodromal symptoms, such as paresthesias, transient aphasia, transient paresis or paralysis and syncope preceded the development of hemiplegia by several hours or days. Optic atrophy with loss of vision on the side of the occluded internal carotid artery was found in some of the cases.

Occlusion of the internal carotid artery is rarely recognized early, so that guides to treatment based on actual experience are lacking. When the internal carotid artery is deliberately ligated for the treatment of intracranial aneurysms and vascular malformations, and complications occur, stellate ganglion block, oxygen, nicotinamide, and papaverin are often used. I have found no record of an attempt to restore the circulation by the surgical removal of a thrombus or embolus from the internal carotid artery. Likewise, I know of no case where heparin or dicoumarin have been used in the treatment of acute non-traumatic occlusion of the internal carotid artery. It is suggested that, if cases of carotid artery occlusion are diagnosed early enough, both methods be tried.

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## AN IMPROVED OSTEOPLASTIC EXPOSURE OF THE TEMPORO-OCCIPITAL REGION\*

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Various adaptations of osteoplastic flaps to the exposure of the frontal, parasagittal and occipital regions, to suit the local anatomical peculiarities of the calvarium, are well known and widely used. On the other hand, an extensive osteoplastic exposure permitting exploration of the middle cranial fossa, especially the base of the temporal and the occipital lobe, has not as yet been worked out. Instead, the customary fronto-parieto-occipital flap is shifted toward the base and somewhat posteriorly, and as much bone removed from the lateral wall of the middle fossa as retraction of the temporal muscle will permit. This type of horseshoe flap has the disadvantage of being widest in the lower fronto-parietal region, where exposure of the brain is not necessary, if not detrimental (as will be shown presently), while the operative field gets increasingly narrow as it approaches the base of the skull where a maximum of room in which to work is needed. This disadvantage becomes particularly apparent in dealing with subtemporal meningiomas, extending over the superior surface of the tentorium, sphenoidal ridge meningiomas, which tend to grow in a backward direction, and tumors of the temporal horn and the atrium of the lateral ventricle. The same applies to more or less concealed basitemporal and basioccipital lesions as, for example, gliomas of the temporo-occipital junction; finally, to those expanding lesions whose location in either the temporal or the occipital lobe cannot for one reason or the other be determined before operation.

Apart from the failure adequately to expose the lesion the old method is potentially dangerous in those instances in which reduction of intracranial hypertension in temporal lobe tumors proves to be impossible at operation, as may be illustrated by the following case.

### CASE REPORTS

*Case 1.* S. J., a 47 year old colored woman, (M. S. H. Adm. No. 540169) was admitted with the chief complaints of fronto-parietal headaches, right orbital pain, a dull aching sensation in the right side of her face, and noises in the ear on that side. Examination revealed bilateral papilledema, a right Horner's syndrome, a diminished right corneal reflex, and a left lower faeial weakness. The greater wing of the sphenoid bone on the right appeared to be mottled and the superior orbital fissure widened. The preoperative diagnosis was right middle fossa meningioma.

*First Operation:* (10/16/45). The right fronto-temporo-parietal region was exposed through the then customary osteoplastic flap and a generous subtemporal decompression added. Following opening of the dura there was marked bulging of the exposed part of the brain into the operative field. Neither canulation of the anterior horn of the left lateral ventricle nor intravenous administration of hypertonic glucose solution reinforced by caffeine sodium benzoate reduced the intracranial pressure to any appreciable degree, and bulging of the exposed part of the brain continued throughout the operation. Retraction of the temporal

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lobe exposed a small part of the lateral surface of a subtemporal meningioma. The superficial Sylvian vein was engorged and displaced upward. Although the patient had lost only a small amount of blood, fall of the systolic blood pressure to 60 mm. Hg. persisted in spite of a blood transfusion and necessitated the termination of the operation as a decompression. Because of the herniation of the temporal and the exposed parts of the frontal and parietal lobes the bone flap could not be replaced. Postoperatively, the patient showed a complete left hemiplegia and hemianesthesia. It is not known whether she had a hemianopsia as well.

*Second Operation:* (11/26/45). Following reflection of the soft tissue flap, the lesion was widely exposed and, as far as could be ascertained, completely removed. The congestion of the Sylvian vein was still present but there was no thrombosis of the vessel. The sensory and motor disturbances which were detected immediately after the first operation disappeared within one year. With the exception of a mild bilateral optic atrophy, the patient does not show any residual disability at the present time.

*Comment:* The postoperative sensory motor paralysis was attributed to a combination of factors, namely, the herniation and distention of the congested sensorymotor cortex in the lower Rolandic region, and to circulatory embarrassment in both the prerolandic and prostriolandic arteries which, during their course from the Sylvian fissure toward the vertex, might have been kinked against the sharp fold formed by the reflected dura. While the arterial hypotension by itself would not explain the involvement of the lower extremity, adequate blood flow to the parasagittal Rolandic region might have depended on the simultaneous flow through both the anterior cerebral artery, which supplies the leg area, and the Rolandic arteries. It is unlikely that the postoperative disturbances were due to the compression of the carotid bifurcation by the anterior pole of the neoplasm, as improvement of the circulation, occurring as a result of the decompression, should have become manifest by gradual improvement of the lower facial weakness rather than the acute postoperative hemiplegic syndrome.

The customary type of operative approach used in the case under inquiry was awkward, inadequate and, whatever the exact mechanism of the damage inflicted at operation, responsible for the disturbances described above. Increased intracranial pressure, particularly when caused by meningiomas, cannot always be reduced by drainage of the lateral ventricle opposite the lesion, as the intracranial hypertension is due chiefly to increased tissue pressure secondary to venous congestion and edema, and the ventricles are apt to be relatively small. Hemorrhages from the dilated veins, particularly the Sylvian vein, may be troublesome and lead to thrombosis of the vessel. It is true that, following evacuation of a major neoplastic cyst, or drainage of sufficient fluid from the opposite lateral ventricle, (which is the lower when the patient is in the lateral recumbent position) collapse of the involved hemisphere may give ample room to carry out the various operative steps following exposure of the lesion. However, relief of pressure is obtained by displacement of the involved hemisphere\* toward the midline, which increases the preoperative midline shift and causes accentuation of abnormal pressure relations in the region of the upper brain stem. The potential danger of this mechanism is well known (2). While reduction of

\* Accentuation of the midline shift in the lateral position of the head, with the involved hemisphere uppermost, can be sometimes demonstrated by ventriculography (1).



intracranial hypertension is preferable to an abrupt change in pressure relations in vital areas, it is obvious that an exposure limiting protrusion of the brain to the tissue in the immediate vicinity of the neoplasm, and decompression rather than compression of the vital centers should be attempted.

Based on the experience with the case described above and similar observations, it appeared to be imperative to the present writer to

(a) limit the operative exposure to the temporo-occipital lobes, in order to prevent herniation of the Rolandic region,

(b) leave the Sylvian vein covered by dura, to avoid damage to this vessel, and

(c) make the baseline of the osteoplastic flap as wide as possible to gain an adequate approach to the base of almost the entire posterior two-thirds of the cerebral hemispheres. (The occipital pole cannot be explored by this approach.)

Subsidiary measures that may or may not have to be taken in order to facilitate exposure of the lesion still further, include the administration of hypertonic solutions and other dehydrating agents, partial resection of the temporal lobe on the right, and the inferior temporal convolution on the left (in right-handed individuals) and, perhaps, evacuation of the beginning of the Sylvian cistern in those cases in which this space is not obliterated. In addition to the protection of the Rolandic region, the most important modification of the customary osteoplastic exploration is the addition of a burr-hole in the supra-auricular region and its connection with a burr-hole placed in the postauricular space. This maneuver has to be carried out without interfering with the blood supply to the base of the flap.

#### ANATOMICAL CONSIDERATIONS

The anterosuperior segment of the temporal line, which can be readily palpated through the delicate skin covering the anterior temporal region, corresponds to the long axis of the second frontal convolution. The superior segment of the temporal line crosses the sensory-motor area at some distance from the Sylvian fissure while its posterior segment sweeps downward and forward to merge with the superior margin of the root of the zygoma. A bone flap following the outline of the temporal muscle would therefore expose the posterior part of the third frontal convolution, the lower Rolandic region and the major portion of the temporal lobe but would fail to uncover the adjacent portion of the occipital lobe. If the temporal lobe is enlarged, the Sylvian fissure is displaced upward and forward and the third frontal convolution as well as the Rolandic and parietal opercula are elevated. In the average case of temporal lobe tumor, the anterior part of the Sylvian fissure may be presumed to coincide approximately with the projection of the temporal line upon the surface of the distorted brain. A bone flap, the outlines of which follow the temporal line, would therefore expose practically the entire temporal lobe, but would not be sufficiently large in the anteroposterior direction to expose the adjacent part of the occipital lobe. For this reason, the flap should extend well beyond the posterior border of the temporal muscle.

## OPERATIVE PROCEDURE

Anteriorly, the skin incision curves downward almost as far as the mid-zygomatic point; anterosuperiorly, it is made to correspond to the line of insertion of the temporal fascia; posteriorly, it extends into the retroauricular region to a point overlying the groove of the lateral sinus (fig. 1). The shape of the skin flap is therefore somewhat unconventional as resembles an early Wagner flap



FIG. 1. Interrupted Line: Customary skin incision prior to reflection of temporo-occipital osteoplastic flap.

Solid Lines: Two separate skin incisions are used for the improved approach to the temporo-occipital region.

Dotted Line: Median plane.

Parallel Lines: Rolandic Fissure.

rather than the current horseshoe type of incision, the wide base of the flap extending from the retroauricular region to a point in front of and slightly above the external auditory meatus. Since the proposed operative site covers some of the anterior and posterior parts of the skull which appears to be foreshortened and therefore somewhat distorted in the recumbent position of the patient, one is likely to misjudge the proper position of the landmarks, and the skin flap should

therefore be outlined with colored antiseptic while the patient is still in the sitting position. In this way one is also in a better position to decide whether the patient should be placed on the operating table in either the prone or the supine position.

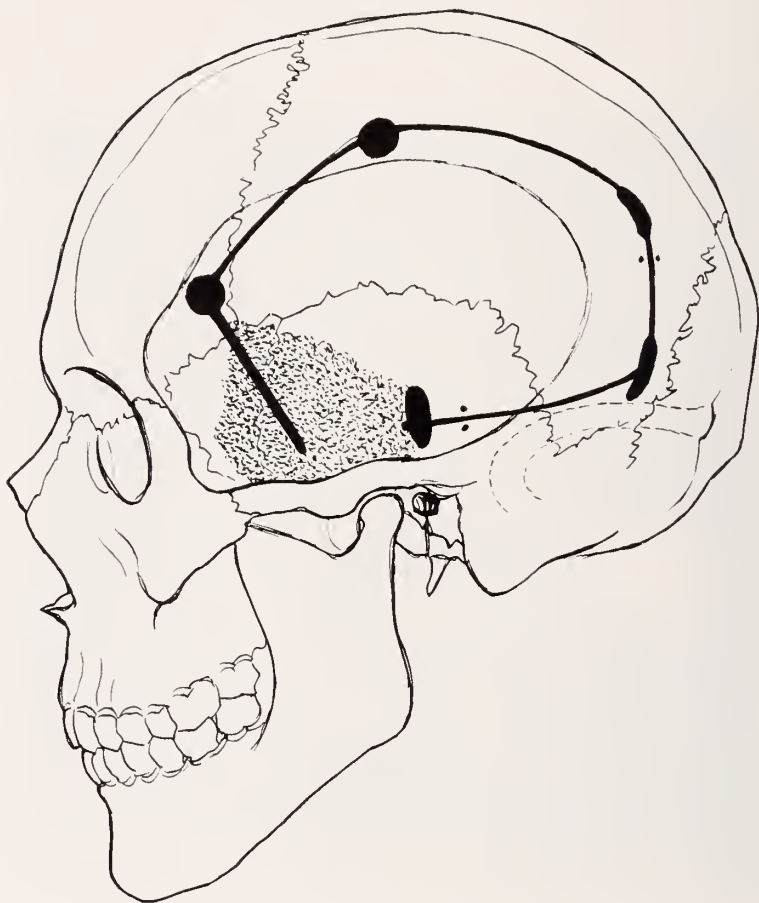


FIG. 2. Stippled area: Subtemporal decompression. Bone is removed both in front and behind the gutter extending from the anterior burr-hole to the base of the skull.

Dots: Drillholes made on either side of the saw cuts connecting the third and the fourth, and the fourth and the fifth burr-hole, for wiring the flap. Anteriorly, proper position of the flap is obtained by suturing both temporal fascia and muscle.

In order that the size and shape of the craniotomy defect may correspond as closely as possible with that of the enlarged temporal and the anterior segment of the occipital lobe, the burr-holes should be placed in the following fashion (fig. 2). The first burr-hole is made just below the temporal ridge in the anterior temporal, the second, above the temporal line in the lower Rolandic region, the third at a somewhat lower plane about  $1\frac{1}{2}$  inches behind the posterior insertion of the temporal muscle; and the fourth, in the retroauricular region. It should be

enlarged toward the base until the superior edge of the lateral sinus comes into view, but the dura overlying the sinus should of course not be uncovered. The anterior fibers of the temporal muscle, which run toward the coronoid process of the mandible in a nearly vertical direction, are split and a narrow gutter is made in the greater wing of the sphenoid bone and the temporal squama. The gutter should reach the base of the skull at the midzygomatic point. Placement of the gutter farther forward may be difficult because of the projection of the pterionic ridge into the cranial cavity. The burr-holes are connected by saw cuts in the usual fashion.

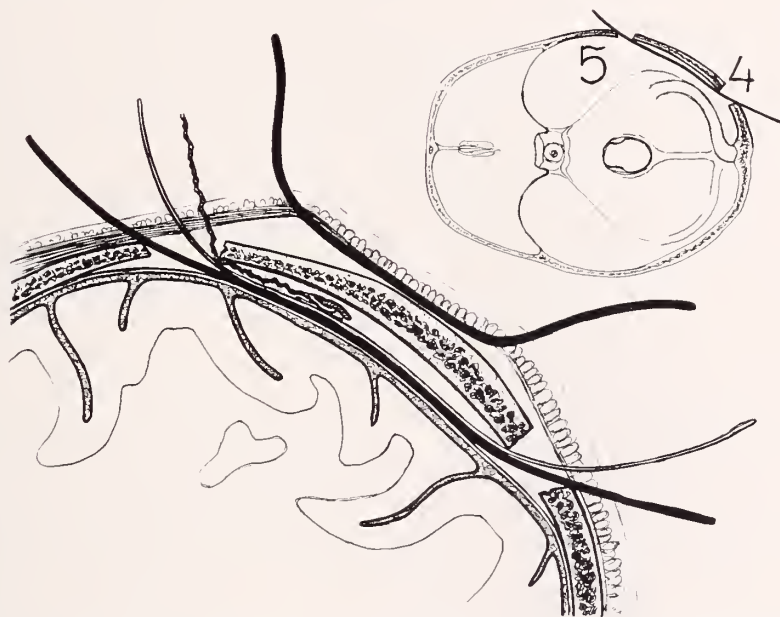


FIG. 3. Method of connecting the retroauricular (4) with the supraauricular burr-holes (5).

Saw guide and Gigli saw are introduced between internal table and dura. As displacement of the saw during connection of burr-holes may injure dura and brain, a ribbon retractor is slid between the former and the saw guide while second ribbon retractor protects soft tissues of skull. Saw guide may be removed once epidural ribbon retractor is in place.

Breaking of this type of flap is, of course, impossible without considerably narrowing its base. Therefore a short vertical skin incision is made separately above the ear, and the dura exposed through a fifth burr-hole. Prior to this, the fibers of the posterior (horizontal) portion of the temporal muscle have to be separated to expose the bone. The incisions into the skin and the muscle are oriented perpendicularly to each other. Both the supraauricular and the lower occipital burr-holes are connected with the Gigli saw. Damage to the overlying skin and the temporal muscle can be avoided in spite of the sharp curvature of the horizontal outline of the skull in the temporo-occipital region by enlarging



the burr-hole and protecting dura, muscle and skin by small flexible ribbon retractors used in combination with the Gigli saw (fig. 3). The separate incisions into the skin and muscle should be closed with a few stitches of fine silk before breaking the flap.

Following exposure of the dura covering the convexity of the temporo-occipital lobes, bone is rongeured away in the anterior temporal region both downward toward the zygoma and as far as the anterior wall of the middle cranial fossa. If the saw cut connecting the supraauricular and the lower occipital burr-holes has been placed sufficiently low to skirt the base of the middle fossa, further bone removal in the posterior temporal and occipital regions is unnecessary; besides, it would leave a poorly protected defect below the thin horizontal portion of the temporal muscle. (This precaution was neglected in the early cases of this series, fortunately without untoward sequelae.) If a more generous decompression is to be carried out, bone should be removed from the anterior inferior portion of the flap where the temporal muscle is strongly developed.

The dura is incised in a curvilinear fashion and reflected upward toward the Sylvian fissure but exposure of the Sylvian vein and its junction with the Rolandic vein, for reasons given in the introductory paragraphs, should be avoided. In the posterior portion of the field, Labbée's vein, connecting the Sylvian vein with the lateral sinus, is seen to cross the surface of the brain.\* The three temporal convolutions are clearly visualized. The anterior part of the craniotomy defect is occupied by the enlarged temporal pole.

Following completion of the intradural part of the operation, the bone flap is reflected and wired in position between the third and fourth, and the fourth and the fifth burr-hole. The soft tissues are closed in the usual fashion.

Like the Frazier flap used to expose the frontal and the anterior part of the temporal lobe, the osteoplastic approach to the temporo-occipital region, as described in this article, is more time consuming than the ordinary osteoplastic flap but, due to the wide exposure obtained and the relative ease with which hemostasis is accomplished, the total operating time is shortened. The additional time spent in doing the bone work prior to operating on the neoplasm is justifiable in surgically favourable lesions but is hardly warranted in frankly malignant lesions particularly on the left side in right handed individuals, where extensive lobectomies are but reluctantly carried out, and replacement of the bone flap may therefore be impossible. The rare presence of large air cells in the supra-auricular region may prohibit to carry out the procedure described.

The applicability of the temporo-occipital flap described in this article may be exemplified by two cases in which the procedure was, however, somewhat modified. In one case, the supraauricular burr-hole was used as an exploratory opening; in the second, the osteoplastic exploration was combined with a sub-occipital craniectomy. Only the essential clinical and roentgenologic findings will be given in the following case reports.

\* Ligation of Labbée's vein may be unavoidable in dealing with lesions of the temporo-occipital junction but does not appear to produce permanent damage either to the optic radiation or the speech area (2).

*Case 2.* M. K., a 59 year old white woman, (M. S. H. Adm. No. 696270) was admitted with the history of transitory impairment of receptive speech following a trivial accident six weeks ago (March 1949). The episode of aphasia was followed by frequent attacks of headaches. Otherwise, the history was noncontributory. On examination, the patient showed a left homonymous hemianopsia, and a left hemihypaesthesia and hemiparesis. There was definite anomia. Within a few days, the patient became increasingly drowsy and, eventually, comatose.

*Operation.* (May 16, 1949). At operation, which owing to the patient's rapidly deteriorating condition, was carried out as an emergency procedure, a burr-hole was made in the supraauricular region and the dura opened. On canulation, definite resistance was encountered approximately  $1\frac{1}{2}$  centimeters below the brain surface. A low temporo-occipital flap was turned down, the dura reflected upward and a part of the right temporal lobe overlying the lesion resected. A hard encapsulated mass, the size of a golf ball, which was connected with the superior surface of the petrous bone by a solid stalk, was dissected out. While numerous traction sutures were inserted into the mass to facilitate its separation from the surrounding brain, a few drops of pus escaped through one of the small holes made by the needle. The firmly encapsulated and grossly lobulated abscess, the presence of which could not have been suspected on clinical grounds, was completely removed. The cavity in the temporal lobe was irrigated with 100,000 units of penicillin and an equal amount of bacitracin, and the wound closed in the usual fashion. The patient regained consciousness on the following morning. The preoperative sensory-motor signs were not increased. Four weeks later, on discharge from the hospital, the sensory-motor disturbances had disappeared but there was still some speech hesitancy, which is gradually subsiding.

*Comment.* As compared to the first case, the lesion occupied a somewhat more posterior position and was probably slightly larger but, on the whole, the two lesions under consideration were comparable as to their gross morphologic aspects. Although we were dealing with a more advanced case of intracranial hypertension and the local signs were likewise more prominent than in the first case, the immediate result of the operation was in every respect more gratifying. This was no doubt due to the type of exposure used which avoided herniation of the Rolandic region and made the removal of the abscess with a minimum of trauma possible.

*Case 3.* F. McG., an 18 year old white man, (M. S. H. Adm. No. 596578) was admitted on April 28, 1949 with a history of petit mal attacks for seven years, fronto-occipital headaches for 18 months, and increasing bilateral deafness for one year. Within the last year, he developed dysphagia, hoarseness of voice, and unsteadiness of gait. The positive neurologic findings included bilateral papilledema of 2 Di., absence of the corneal reflexes on either side, a right lower facial weakness, bilateral impairment of hearing of central type, nystagmus on left, right, upward and downward deviation, and involvement of the 9th, 10th and 12th cranial nerves on the left. There was definite ataxia on station and gait, and the finger to nose test was poorly performed bilaterally. X-ray examination of the skull disclosed a left parasellar calcification, widening of the internal auditory meatus and erosion of the apex of the petrous bone on that side. The right half of the atlas was absent. Angiography performed on the left showed the terminal portion of the internal carotid and the beginning of the middle cerebral artery to be straightened out and displaced forward, and the Sylvian vessels to be elevated. The diagnosis of a neoplasm occupying both the left middle and posterior cranial fossa was made and a two stage approach to the lesion planned.

*First Operation* (May 12, 1949). As expected, suboccipital craniectomy revealed absence of the right half of the atlas but, with the exception of displacement of the cerebellar vermis

to the right, and marked tonsillar herniation, chiefly on the left, there were no pathologic findings in the region of the cisterna magna. On further exploration, a grape-like mass covered by many large veins was encountered in the superolateral portion of the left posterior fossa. Removal of this mass was difficult because of the great vascularity of the individual lobules of the neoplasm and the size and congestion of the intervening blood vessels. Largely because of this vascularity, but also the unfamiliar aspect of the lesion which made it impossible to predict its behavior at operation with a reasonable degree of certainty, the procedure was terminated at this stage. Histologic examination proved the lesion to be a leptomeningioma.

*Second Operation (June 9, 1949).* A low temporo-occipital flap was turned down on the side of the previous operation, the dura was reflected upward and, as the lesion failed to present on the lateral surface of the hemisphere, the third temporal convolution was resected. Gentle retraction of the remaining part of the temporal lobe from the base of the



FIG. 4. See text

skull exposed a typical meningioma which occupied apparently the entire superior surface of the tentorium, most of the superior surface of the petrous bone and the parasellar space, where it was intimately adherent to large blood vessels. The anterior pole of the lesion evidently corresponded to the parasellar calcification seen on the X-ray films. Except for this part of the neoplasm, the lesion was removed with the electrosurgical loop and the superior surface of the tentorium laid bare. Expecting to determine the size and location of the infratentorial part of the lesion more precisely than could be done at the first operation, an opening the size of a five cent piece was cut into the tentorium midway between the petrous ridge and the lateral sinus. As far as could be ascertained, the remaining infratentorial portion of the tumor was of considerable size and it was therefore decided to make a final attempt to deal with the neoplasm through a combined supra- and infratentorial approach, although the possibility of its being radically removable appeared remote.

*Third Operation. (7/11/49).* With the patient in the upright position, the transverse sub-occipital incision was reopened, and the skin overlying both occipito-parietal regions

was reflected upward, the base of the skin flap corresponding to the vertex of the skull. In order to connect the supratentorial with the infratentorial operative field, the following parts of the left side of the calvarium were temporarily blocked out: a portion of the squama of the occipital bone lying between the midline and the osteoplastic temporo-occipital flap, the posterior one third of the flap, and the bone lying on either side of the lateral sinus. After ligation and partial resection of the lateral sinus, reflection of the dura from the temporo-occipital region and elevation of the occipital lobe, tumor tissue which filled a large part of the posterior fossa and was intimately adherent to the compressed cerebellum was removed. Electrosurgical removal of the lesion and mobilization of its mesial portion was continued until the lateral surface of the pons was brought into view.

For fear of damaging vital structures, neoplasm extending from the region of the mouth of the great vein of Galen along the tentorial notch to the parasellar space, and along the posterior surface of the apex of the petrous bone to the jugular foramen was left behind. Even so, the size of the cavity produced in the left posterior fossa by the subtotal removal of the lesion indicated that the brainstem had been extensively decompressed. The three fragments of the calvarium that had been blocked out were wired in position, (fig. 4) and a large periosteal flap taken from the right occipito-parietal region sutured to the soft tissues surrounding the irregularly shaped supratentorial craniotomy wound. The infratentorial cavity was drained and the wound closed in the usual fashion. The patient withstood the six hour procedure well, and his condition on discharge (Aug. 3, 1949) appeared generally improved. Both the subtemporal and suboccipital decompressions were flat and soft.

*Comment.* The absence of the right half of the atlas was presumably a congenital malformation; otherwise, the roentgenologic and clinical findings could be easily correlated. A somewhat larger osteoplastic flap would have saved much bone work at the third operation and had shortened the time spent for the closure of the wound. An improved two stage combined approach could be advantageously employed for acoustic neurinomas, meningiomas and cholesteatomas extending from the posterior into the middle fossa although a radical removal of the lesion will not always be possible. A one stage combined supra- and infratentorial approach through a single large osteoplastic flap has been in use at various clinics for some time, and transtentorial (transtemporal) removal of acoustic tumors has also been attempted. The present writer has no experience with these procedures, but it would seem that a combined two stage exploration would be preferable in dumbbell meningiomas and cholesteatomas which, unlike acoustic tumors, may attain a huge size both above and below the tentorium, as exemplified by the above case.

It is suggested that in cases of this kind, the supratentorial portion of the lesion be attacked first and the retroauricular burr-hole, in order to take full advantage of an extensive basal exposure, be placed as far posteriorly as possible. After an appropriate interval the infratentorial portion of the lesion may be dealt with by a wide suboccipital craniectomy.

#### SUMMARY

1) An improved osteoplastic exploration permitting exposure of the entire temporal and most of the occipital lobe, including the basitemporal and basioccipital regions, is described.



2) Undesirable effects of incorrectly placed temporo-occipital osteoplastic flaps are discussed.

3) Attention is called to the combination of the temporo-occipital osteoplastic exploration and a suboccipital craniectomy, which may be advantageously used for the exposure of certain dumbbell tumors occupying both the middle and posterior cranial fossa.

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## DEPRESSED FRACTURE OF THE TIBIAL PLATEAU\*

### A SIMPLE SURGICAL METHOD FOR ELEVATION AND FIXATION OF THE DEPRESSED FRAGMENT

ROBERT K. LIPPMANN, M.D.

Dr. Berg's great early interest in bone grafting was reflected not only in his important experimental work concerning the osteogenetic properties of the transplant but also in his pioneer clinical use of the bone graft as a replacement device (1, 2). Recent conversations have indicated that this early interest in the graft endured in spite of the diversion of the main flow of his energy and skill into the intricacies of the viscera. The present report concerns an application of the cortical graft which to my knowledge has not yet been described and which, I believe, would have been of interest to him.

In most cases, the bone graft is employed for a dual purpose—that of stimulating osteogenesis and that of providing interim immobilization or support. On occasion, however, the device is used purely for the stimulation of osteogenesis. In the Hibbs type of spinal fusion, for example, the early graft is expected to contribute no supportable function. The application to be described utilizes a cortical graft not for its osteogenetic property but purely as an interim support or prop—useful until the surrounding skeletal tissue reaches a stage of repair adequate to resume this function.

#### THE TYPES OF PLATEAU FRACTURE AND THEIR MECHANISM

The “bumper” fracture or fracture of the outer tibial plateau described by Cotton (3) in 1929, results from the impact of the femoral condyle upon this structure generally following a lateral blow close to knee joint level. Watson-Jones (4) has offered a useful classification of these fractures into two types. The first consists of those relatively uncomminuted fractures in which the entire tuberosity is detached, depressed, and impacted. The second type of fracture is more complicated and usually more severely comminuted. In these fractures, one or several central fragments are driven directly downward and impacted more or less deeply into the cancellous bone of the tuberosity. As the femur descends for the impact, one or more lateral flanges are spread apart and hinged outward by the bulk of the condyle. As the femur recedes, however, they return to approximately normal position clamping the depressed fragment or fragments in the depths of the cancellous bone. Only occasionally do plateau fractures occur that present the features of both varieties. While both types of plateau fracture are produced by the downward thrust of the condyle, it would seem that the first type of fracture is produced by a blow distributed broadly throughout the condylar area, while the second type must be the result of a more sharply centrally concentrated impact. The first type of fracture is therefore the more likely

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injury when the blow is received with the knee joint extended; the second type when the knee is in the position of flexion (fig. 1).

The plateau fracture of the first type generally presents little therapeutic difficulty. Even though the x-ray may disclose severe damage, the intact lateral ligament renders manipulative control possible. Reduction by manipulation can usually be effected and the corrective position maintained either by bolting or by plaster immobilization (fig. 2). The therapy of fractures of the second type present a far more difficult problem and constitute the subject of the present

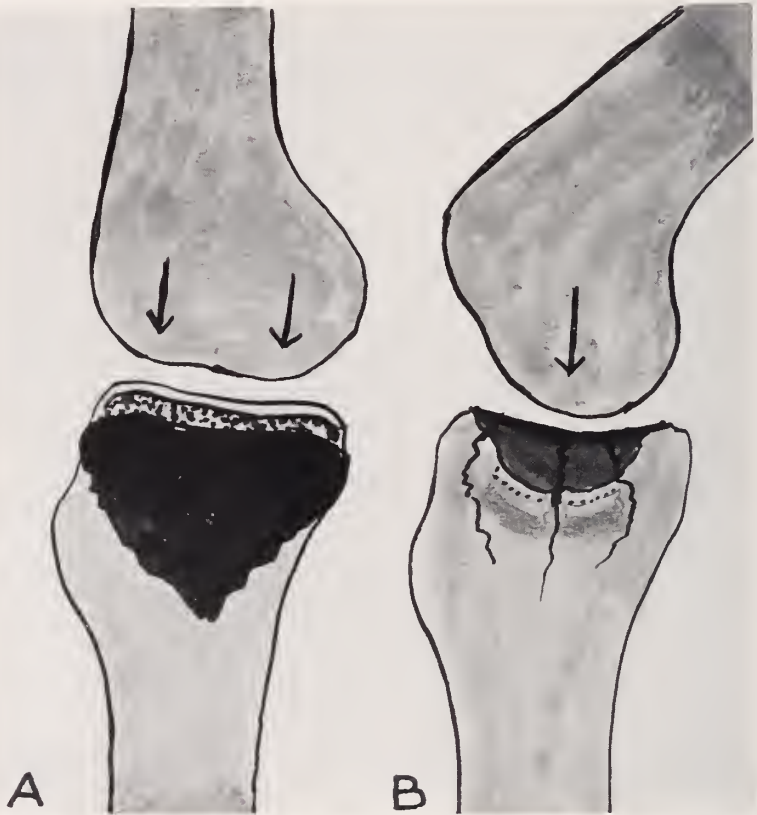


FIG. 1. The two types of plateau fracture and the probable mechanism of each

- A. The first type—the knee in extension.
- B. The second type—the knee in flexion.

report. In these fractures manipulative reduction is obviously impossible. The choice rests between acceptance of the malposition and open reduction and fixation. In this choice, opinions vary as widely as the varieties of operations recommended for the purpose.

#### SURGICAL CRITERIA

In fractures of the second type with minimal displacement, there is general agreement that the final result is better following conservative therapy. The

replaced lateral flanges heal to the main shaft and take over the supportive function of the depressed elements. Bick (5) has demonstrated that the lateral laxity which is often the immediate aftermath improves considerably with time and, at the end of a year or so, may completely disappear. The inevitable late osteoarthritic changes are generally not as severely symptomatic as might be expected.

For those fractures with more severe displacement, surgical criteria are at wide variance. Watson-Jones recommended open reduction only when absolutely unavoidable and cautioned that even more significant late changes can follow the increased deprivation of blood supply that surgery entails when indiscriminately employed. In this view, he was in close agreement with Cotton (3) in his original report upon this type of fracture and with a number of other writers on the



FIG. 2. The gratifying replacement that may be obtained by simple manipulation in plateau fractures of the first type even though severely displaced and comminuted.

- A. Original fracture dislocation sustained after being thrown from a motorcycle.
- B. Four months after injury.

subject (Magnuson (6)). Barr (7) has stated that when "displacement exceeds one-half inch" surgical replacement is indicated and Campbell (8) in his text book implied agreement with this figure. Kennedy (9) recommended surgical reduction when depression is greater than three-sixteenths of an inch, or if the depression involves more than fifty per cent of the condyle. Leadbetter (10) on the other hand, impressed with the frequency with which late symptoms develop when significant malposition is accepted, presented the case for broader surgical criteria. Our own experience, in accordance with Leadbetter's, would indicate that pain, lateral laxity, stiffness, and valgus deformity are by no means rare sequelae of these injuries. As in all fractures involving important joint surfaces, accurate reduction is plainly of the greatest importance, provided it can be accomplished without excessive and destructive surgery. The difficulty lies in the



repeated failure of the simpler recognized methods such as chip grafting to maintain the re-elevated fragments in corrected position and the recognition that a more trustworthy support is required (Key (11) and Dickson (12)).

Unfortunately, many of the mechanically ingenious and effective procedures that have been devised for this purpose entail extensive dissection and the risk of further compromise of blood supply. Knight (13) has employed interlaced match stick grafts reinforced by Knowles pins. Cave (14) recommended a transverse cortical graft supported by a through and through bolt. Heavy metal blocks in a variety of shapes have been also designed for incorporation in the bone to provide support for the re-elevated bone fragments. Certainly revascularization can be hampered by the dissection required for such major operations as these as well as by large incorporated metallic devices. It is not surprising that the eventual result is increased joint compromise rather than improvement.

The procedure herewith submitted appears to overcome many of the objections to the more complicated methods now in use. It is easy to perform and provides a firm supporting strut under the replaced fragment. The graft may be inserted with a minimum of surgical trauma and without need for supplementary bolts or other reinforcements. For these reasons, the method can be safely utilized to extend benefits of accurate reduction, to the less severely displaced fractures as well as to those in which operative reduction is imperative.

#### TECHNIC

Under tourniquet control, a four inch vertical incision is developed antero-laterally high enough to provide for inspection of the outer meniscus and its removal, if necessary. Inspection of the articular surface practically always reveals a crack that radiates anteriorly from the depressed fragment and continues downward along the anterior tibial surface. The dissection follows downward in the line of this crack with minimal sub-periosteal elevation. If the bone fragments separated by the crack are still firmly bound to each other, a quarter-inch hole is drilled through the cortex in line of the crack about a half-inch below the joint surface. This site is chosen when possible because it avoids further compromise of vascularity. However, if the fragments move freely with reference to each other, the hole is drilled slightly toward the mesial side. A small curette may then be inserted into the hole and employed as a lever to pry the depressed elements up into normal relationship (fig. 3A). With the hole as a starting point, a narrow rongeur is used to convert the hole into a vertical slot a quarter-inch wide extending up to the joint surface and down an inch or so until the cortex becomes thick and sturdy (fig. 3B). Through a separate incision, a cortical graft is removed a half-inch wide and one-half inch longer than the slot that has been created in the tibia. The graft is then shaped as illustrated in figure 3C.

The notch at the base of the graft is hooked over the cortex at the lower pole of the slot and its upper aspect impacted toward the slot (fig. 3D) until its upper margin is close to the tibial slot. At this point, a double action cutting pliers is used to give the top of the graft its final trimming in length. This must not be short, as the graft is designed to lie directly under the subchondral cortex of the

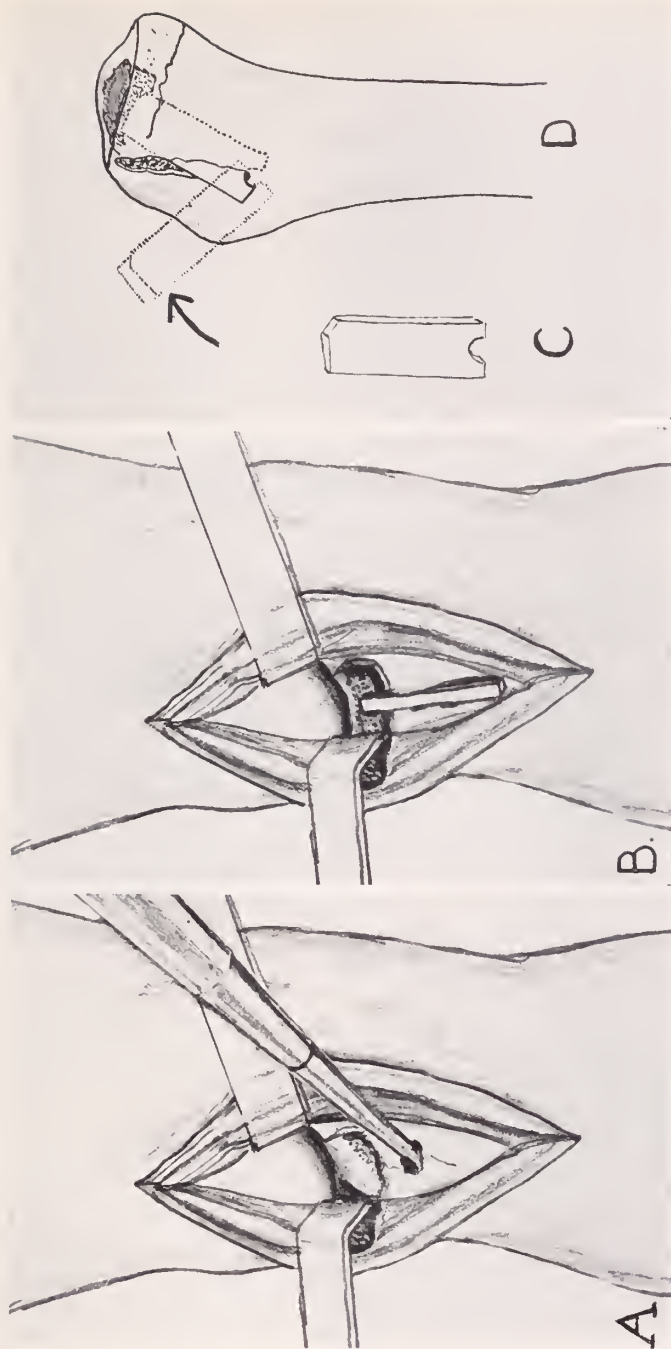


FIG. 3. The operative procedure

- A.\* Elevation of depressed elements using small curette as a lever.
- B.\* The final position of the cortical strut. Note that it reaches upward to subarticular cortex. A shorter graft which reaches only to the level of the cancellous bone of the fragment is insecure.
- C. The shape of the graft.
- D. The method of inserting the graft through the slot. After hooking it over the slot's lower pole, it is impacted into place after the upper end of the graft is accurately trimmed to the correct length.

\* Illustrations A and B show bone over the depressed fragment pulled aside for better visualization.



FIG. 4. Illustrative case in which the strut graft was employed

A. Original injury.

B. Two months after operation. Plaster removed.

C. Four months after injury. "Spreading" of the graft denotes revascularization. Complete revascularization also apparent in the texture of the cancellous bone throughout the damaged area. Complete joint stability was present. Flexion to eighty degrees.

depressed fragment—not its subjacent cancellous bone. After this final adjustment, the graft is impacted home, its upper end directly underneath the previously depressed area. This final position may be checked by direct vision through the slot and confirmed by the application of firm downward pressure upon the re-elevated elements through the joint.

The graft is so well braced by the lower intact trabeculae and by the cortex that no additional support for it is necessary. The lower anchorage of the graft upon firm cortex precludes any possibility of downward displacement. Our practice has been to follow the operation with plaster immobilization for two months and with the avoidance of weight bearing for an additional month. Quadriceps exercises are useful during these stages of revascularization and convalescence. In the first case illustrated (fig. 4) the maintenance of position is noteworthy as is the rapid and complete revascularization attained. Figure 5



FIG. 5. Illustrative case #2

A. Original fracture.

B. Medial shift of the graft due to complete fracture of the lateral flange.

illustrated an oblique graft placement, utilized when the lateral flange is completely fractured.

#### SUMMARY AND CONCLUSIONS

The outer tibial plateau fracture with depression of fragments can produce lasting sequelae even when displacement is less than extreme. As in all intra-articular displaced fractures, the tibial plateau fracture does best when reduction is effected. The difficulty rests in the formidable procedures that have been necessary for reduction and maintenance of position. Were a simple and trustworthy method available, the benefits of reduction could be accorded not only to the most severe cases but to those of only moderate severity as well. A simple procedure is presented which maintains firm and secure elevation of the depressed condylar elements. It has the advantages of minimal additional disturbance of



the fracture area and requires no supplementary bolt or fixative material. The method should be applicable to a wider range of plateau fractures than many of the complicated procedures now in use.

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# LIPOMA PETRIFICUM OSSIFICANS OR LIPOMA WITH HETEROTOPIC OSSIFICATION\*

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This title was taken from Ewing's Pathology of Tumors, where, in turn, it was attributed to Virchow, without any intermediate references. It is well known that lipomata may undergo degenerative changes varying in character, including that of diffuse calcification and ossification. Many a pathologist has informed me of having encountered similar cases in their own experience, which, however, they have not considered sufficiently important to report. The literature on lipomata is quite profuse and old, yet in the last 10 years there have been no papers on calcification or ossification in such tumors. Most of the pathology texts do not even mention this degenerative change or dismiss it with a line or two. Even in Ewing's textbook, only a brief paragraph mentions the entity as well known from Virchow's day on, and gives the descriptive title as above.

In the great bulk of cases, lipomata are superficial, easily diagnosed and present little difficulty in therapeutic indications. However, in the uncommon cases of deep lipomata, diagnosis may be very difficult prior to surgical exploration. I have recently treated a case in which not only was the lipoma deep but diffusely and irregularly ossified so that the diagnosis was missed entirely. The clinical fact of the ossification was preeminent and confused the therapeutic indication so that surgical exploration and excision of an extensive malignant tumor was projected until exploration revealed the true state of affairs. Shortly after the first case, I encountered a second case in which the pathology was identical with the first. However, here the tumor was superficial, the bony structure easily palpable and the correct diagnosis and treatment carried out in straightforward manner.

## CASE REPORTS

*Case 1. History.* L. H. was a 55 year old woman who was admitted to the Bronx Hospital on January 21, 1949. Her complaint was a mass in the right groin, of 20 years duration, originally small, and gradually enlarging. It was said to have grown more rapidly in the preceding year. There were no associated symptoms. Her previous medical history included a subtotal thyroidectomy 10 years before, a mastoidectomy complicated by a thrombophlebitis of the right leg, appendectomy and hysterectomy 1½ years before. She had had four children without complication.

*Physical examination.* Except for the local condition in the right groin, nothing was noted. There was a hard, rounded, smooth, non-tender, immobile, deep mass, larger than an egg, in the right inguinal fold and upper thigh. It was most protuberant 1½ inches medial to and below the anterior superior spine of the ilium. It was deeply adherent either to the pubis or hip structures anteriorly. There was no local skin tenderness nor other change.

*Laboratory.* Studies were entirely normal apart from the xray findings. X-ray of the chest was normal. X-ray of the right hip, made in anteroposterior and lateral projections, showed an irregular mass of calcifications and ossifications overlying the front of the hip joint and extending from above and lateral to the femoral head to below and medial to it. The hip

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\* From the Orthopedic Service of the Bronx Hospital.

structures were uninvolved in themselves, the bone and joint outlines being normal as seen through the mass of ossifications. It was noted that on the lateral, taken in the frog position,



FIG. 1. An A.P. view of the pelvis, showing ossifications overlying right hip joint.



FIG. 2. Lateral view of right hip, showing ossifications anterior to the hip joint.

the mass of ossifications seemed to move with the head and neck of the femur as compared to the pelvis adjacent (figs. 1 and 2).

*Preoperative diagnosis* varied from myositis ossificans of a very unusual variety and in an unusual location, to osteochondroma of the pubis or upper femur, or sarcomatous de-

generation (osteogenic) of an old benign tumor, etc. The true diagnosis was not even approximated.

*Operation.* On January 24, 1949, the lesion was exposed by a Smith-Petersen incision, anteriorly over the right hip. The sartorius muscle was found to be displaced laterally by a well encapsulated mass, containing fat, and a large number of irregular plaques of bone. It lay between the sartorius and iliopsoas and was attached by a narrow stalk to the anterior hip joint capsule. It was easily enucleated and the wound closed in the usual manner. Postoperative healing was uneventful and the patient has remained well to date without recurrence.

*Pathologic report.* The gross description was that the mass was pinkish yellow and measured 12 x 6 x 6 cm in size, being irregularly ovoid. The fat itself was soft in consistency. Throughout the specimen, however, many areas of bone were encountered. The cross section could not be made except by sawing through the tumor. Microscopically, the tissue

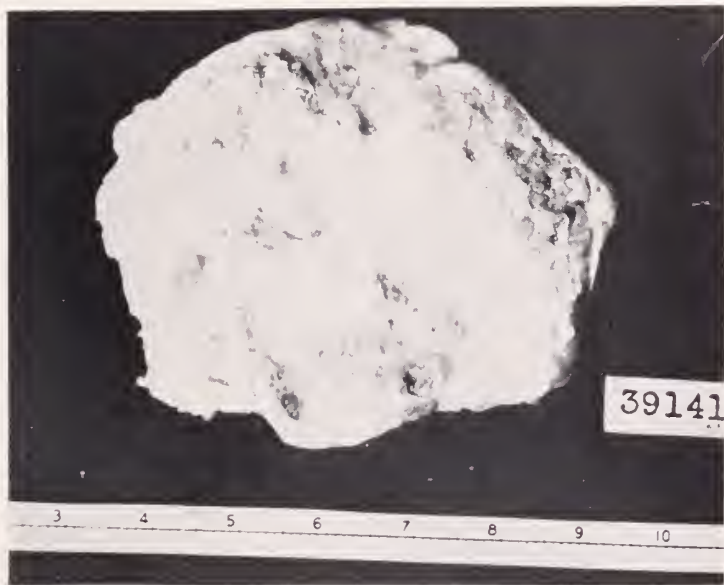


FIG. 3. The tumor removed from the right hip region.

consisted of fat containing bony trabeculae in irregular plaques. The bone was cancellous with fatty acellular marrow (fig. 3).

*Case 2. History.* P. C. was a 50 year old woman who had noted a lump on her back for many years. She had no symptoms associated with it except for gradual increase in size. She was anxious to have it removed for fear of malignancy. Other history was irrelevant. She was first seen on June 24, 1949.

*Physical examination.* Except for the local condition, nothing contributory was noted. There was a hard mass about two inches in diameter in the right dorsal region, paravertebral, at about the level of the eighth dorsal vertebra. It was somewhat flattened antero-posteriorly and roughly circular otherwise. It could easily be felt to contain numerous irregular plaques of bone. It was freely movable on the underlying tissues but was somewhat adherent to the skin. There was no local tenderness. X-ray examination was made but on the AP the lesion could not be seen through the underlying lung and ribs. On the lateral view, in profile, ossified plaques could be faintly seen through the mass where it did not overlie the spine.



*Operation.* Especially in view of Case 1 which had been seen fairly recently, the diagnosis of lipoma with ossification was made and proved correct. It was excised at Bronx Hospital on July 5, 1949 under local novocaine infiltration. It was a  $2\frac{1}{2}'' \times 2'' \times 1''$  in diameter, roughly ovoid and there was some adhesion to skin and deep fascia. However, overall it was quite well encapsulated and easily shelled out. Postoperative healing was uneventful.

*Pathological report.* The lesion was described as a flattened pinkish-yellow hard encapsulated lesion consisting of what looked like cancellous bone with a small amount of adipose tissue interspersed. Microscopic section showed widely separated thin trabeculae of normal bone with fatty marrow spaces between. It was called an osteolipoma, perhaps a misleading term, which might be construed to be a lipoma occurring within a bone.

#### DISCUSSION

The ossification of the lipomata in the two patients presented is an example of "heterotopic ossification". Many different types are mentioned in the literature. These are enumerated by Leriche and Policard as muscle osteomas (localized myositis ossificans); ossifications in vessel walls and hematomas; in the interior of injured nerves; about necrotic foci of all sorts where preliminary calcification has been known to occur frequently; about calcified cartilages in soft tissue, in the uterus, bronchi, trachea, costal cartilages, etc.; in scars in skin and subcutaneous tissues; and finally, in tumors of various sorts such as mixed tumors, growths with zones of necrosis and calcification within them, and even pedunculated osteomata in organs where there never is bone such as the intestine, the fallopian tube, and the thyroid. No specific mention is made of ossification within lipomata but this is obviously included in the last category above.

These authors state that certain factors are always present in heterotopic ossifications; that is, there must be 1) formation of an ossifiable medium in young connective tissue or connective tissue undergoing "embryonic changes" due to organization of a blood clot, or infectious or traumatic inflammation, and 2) a local excess of calcium as in presence of bone, or in organized calcific deposits chiefly occurring in areas of low metabolism or vitality or necrosis in all sorts of conditions such as old tuberculous foci, lithopedions, calcified goitres, necrotic tendons, aponeuroses, fibrinous deposits, etc.

Once these conditions have been satisfied, ossification can occur anywhere. The shape and size depends on the architecture of the tissue in which it develops. The bone formed is identical with normal bone. The ossifications may be absorbed, or more often, be preserved by reason of occurrence in regions of relatively low vascularity surrounded by fibrous tissue capsules, etc.

A similar discussion of the pathogenesis of heterotopic calcification and ossification is given by Barr, and by Watson-Jones and Roberts. The latter go further and attempt to explain the actual deposition of the calcium and then the bone on a humoral and enzymatic basis, influenced by the local pH of the blood and tissues, and by hormones. This was also hypothesized by Leriche and Policard. All the authors are agreed, however, that the exact chemical and physical details involved are as yet incompletely known and incompletely controllable experimentally in laboratory experiments. An extensive bibliography is given.

According to these theories, in the present cases, we must hypothecate the long existence of a lipoma, gradual diminution of the blood supply with slow growth, central necrosis or devitalization of part or all of the tumor, deposition of calcium, and finally, perhaps with new relative increase in the blood supply, ossification of the lesion.

A careful search of pathology texts, works on x-ray diagnosis in bones, joints, and soft tissues, and specific papers on heterotopic ossifications reveals that the only specific mention of ossified lipomata is that in Ewing's work on tumors. The clinical significance of such tumors, especially when the ossification is in a deep lipoma, overlying bones, joints or other organs and tissues and noted on x-ray films of the various parts has never been pointed out. In the present case 1 the diagnosis was not suspected until surgical removal of the lesion, whereas in case 2, where the growth was superficial, the diagnosis was made clinically and confirmed by x-ray study and surgical excision.

#### SUMMARY

1. Two cases of old lipomata with heterotopic ossification have been reported.
2. The difficulty of diagnosis in deep lipomata has been emphasized.
3. The presence of diffuse ossification in the lesion further confused the diagnosis in the deep case (1), and lipoma was not diagnosed until the time of surgical exploration.
4. In superficial ossified lipomata, as in case 2, the diagnosis is much more easily made, as the bone can be palpated and then confirmed by x-ray study and excision.
5. A brief review is given of the various common types of heterotopic ossification and of their pathogenesis so far as is known, with reference to more complete discussions of these aspects.

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## HYPERPARATHYROIDISM

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The observation reported here illustrates that hyperparathyroidism due to a hyperfunctioning parathyroid adenoma may give rise to many different clinical syndromes. The clinical course observed in this patient emphasizes once more that in every patient with renal stones the possibility of hyperparathyroidism has to be considered even if careful x-ray examination does not reveal any bone lesions. In this patient, after two attacks of renal calculosis, unexplained pains in the back and lower limbs developed, but the diagnosis of hyperparathyroidism was made only at a late stage because for years the x-ray picture of the skeleton was apparently normal. This patient is of special interest because two hyperfunctioning adenomas were present and because the removal of the parathyroid adenomas led to healing of a subcapital fracture of the femoral neck.

### CASE REPORT

This patient, Mrs. A. W., Adm. #581874, aged 49 years, colored, was admitted to the Neurological Service of the hospital in November, 1946 and in February, 1947, for the investigation of a severe, right-sided, sciatic syndrome. She had a history of having lifted an extremely heavy object about 8 years prior to her admission, and developing severe "knife-like" pain in her back while doing so. This pain lasted only for a short time then, but subsequently recurred at frequent intervals, and for varying periods of time. In February, 1946, she had lifted a child, and this precipitated another attack of back pain which was quite severe. Several months later, the pain returned and gradually progressed in severity, eventually confining the patient to bed most of the time. At first, there was no radiation of the pain, but later on, it began to spread down the posterior aspect of the right lower extremity, first to the knee, and then to the ankle and toes. A fracture board relieved the discomfort somewhat, but the pain was made worse by coughing, straining, or bending.

Her past history included a left nephrectomy for calculous pyelonephritis in 1943, and an episode of right pyelonephritis secondary to a right ureteral calculus, in August of 1946.

Examinations during her first two admissions revealed slight atrophy of the muscles of the right calf, positive Lasègue and Patrick signs on the right, limitation of straight leg raising to 35° on the right side, but no significant neurological abnormalities, and no spinous or sacro-iliac tenderness. An incidental finding was the presence of a moderate sized, soft enlargement of the right lobe of the thyroid gland, without any clinical signs of thyrotoxicosis. Aside from these findings, physical examinations were completely negative.

Routine blood counts, urine analyses, and blood chemistries were all within normal limits. She did have a moderate degree of renal damage, as evidenced by an excretion of only 30% of the injected phenolsulphonphthalein in two hours, and by an inability to concentrate her urine above a specific gravity of 1.010 on repeated urine concentration tests. Two lumbar punctures revealed the cell count, protein content, and circulatory dynamics of the spinal fluid to be normal. X-ray studies of the chest, skull, spine, pelvis, and abdomen were normal on both admissions. No abnormality in any of the bones was seen, other than a small island of bone condensation in the left iliac bone, adjacent to the left sacro-iliac joint. A lumbar myelogram was done on each of the admissions, and both were reported as showing no significant abnormality. An intravenous pyelogram, of course, showed the absence of the left kidney, but failed to reveal anything wrong with the remaining one. An alkaline phosphatase, done during the second admission was 19 King-Armstrong units per 100 cc. of serum which is only very slightly elevated.

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Although the patient's history was thought to be typical of a herniated intervertebral disc on the right side, the absence of any definite neurological findings, the normal myelograms, and the impaired kidney function all militated against any active surgical intervention, and she was treated conservatively, with bed rest and a back brace. These seemed to help the patient each time she was in the hospital.

However, their effects were relatively short-lived, and her third admission to the hospital took place in June, 1948. She had been comfortable for about three months after her previous discharge, but the pain gradually returned, so that for the 8 or 9 months preceding her last admission she had been confined to bed most of the time.

Examination and routine laboratory studies were exactly the same as they had been on her two previous admissions, and for the first week or so, the same diagnoses were considered as had been discussed before.



FIG. 1a. Subcapital fracture of femur. Severe demineralization. Calcium content of bone decreased so that normal contrast between cortex and medulla of femur has disappeared.

FIG. 1b. Two years after removal of 2 parathyroid adenomas. Complete consolidation of subcapital fracture. Reconstruction of cortex and cancellous bone of the femur.

Great was the surprise, therefore, when x-ray studies of the bones now revealed a generalized osteoporosis, with large "soap-bubble"-like cystic areas present in the outer halves of both iliac bones, and throughout both femora. There was a coarsening of the trabecular pattern within the ribs, with numerous small lytic areas. There was marked decalcification of the cortices of a number of the bones, especially in the metacarpals and phalanges of the hands (Fig. 3a). The skull was diffusely decalcified (Fig. 2a), and islands of bone condensation were seen in the left ilium, left pubic bone, and the left side of the sacrum. These changes were all considered to be compatible with a diagnosis of hyperparathyroidism.

Consequently, blood was drawn, and the results were as follows (table 1): Serum calcium—16.4 mg %; inorganic phosphorus—3.6 mgm %; alkaline phosphatase—57 King Armstrong units per 100 c.e. serum. The Sulkowitch test for urinary calcium was strongly positive even while the patient was on the Bauer-Aub low calcium diet. The results of the calcium excretion studies in the urine on this diet were just within normal limits, the



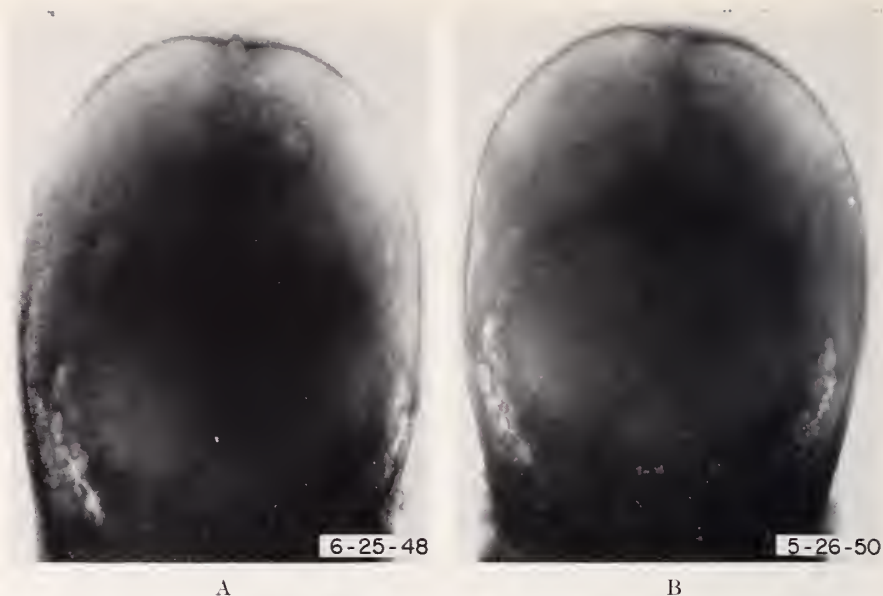


FIG. 2a. Skull in hyperparathyroidism with numerous small areas of bone resorption due to osteitis fibrosa and osteoclastic destruction.

FIG. 2b. Two years after removal of 2 parathyroid adenomas. The bone structure of the calvarium has returned to normal.

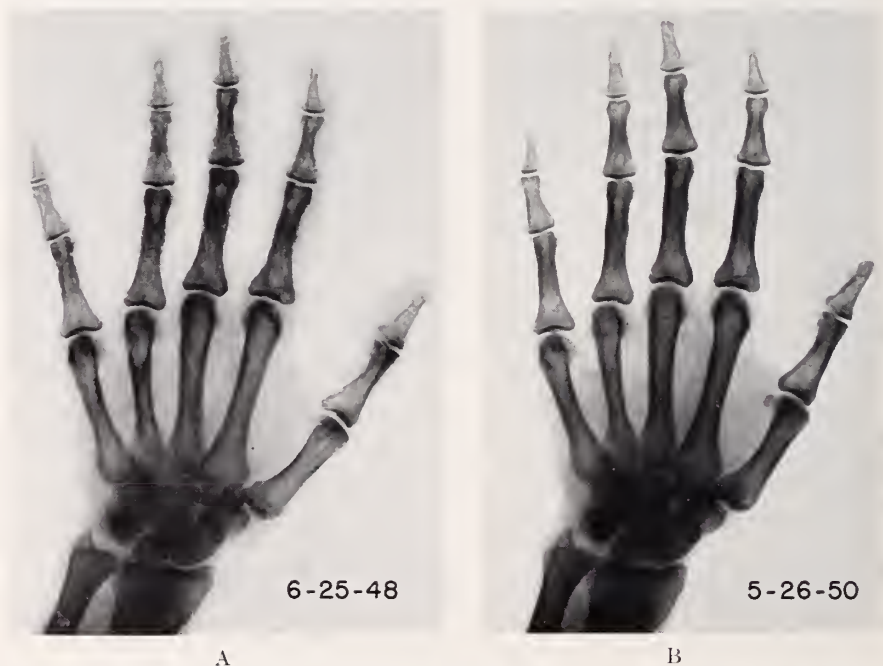


FIG. 3a. Metacarpals and phalanges in hyperparathyroidism. Generalized decalcification with erosion of bone cortex, especially in phalanges.

FIG. 3b. Two years after removal of 2 parathyroid adenomas. Complete reconstruction of cortex and cancellous bone.

patient excreting 418 mgm of calcium in three days. When the serum calcium and phosphorus levels were repeated, the serum calcium then was 17.0 mgm, the inorganic phosphorus 3.0 mgm, and the alkaline phosphatase 72 King-Armstrong units per 100 c.c.

Since it was obvious that the patient was suffering from hyperparathyroidism with renal and bone involvement, surgical exploration of the parathyroid glands was considered necessary, and on July 16th, 1948, she underwent this procedure. In addition to finding adenomatous changes in both lobes of the thyroid, a tumor of the left lower parathyroid gland was discovered and removed. The mass measured about  $1\frac{1}{4}$  inches in length, and was situated behind the lower pole of the left lobe of the thyroid, in close proximity to the

TABLE I

DATE	CALCIUM (mg %)	INORGANIC PHOSPHORUS (mg %)	ALK. PHOSPHATASE KING-ARMSTRONG UNITS
Feb. 4, 1947			19
June 16, '48	16.4	3.6	57
July 1	17.0	3.0	72
July 16	First parathyroid	adenoma removed	
July 20	17.0	—	54
July 22	17.1	1.8	50
July 30	18.5	1.8	80
Aug. 9	—	1.1	82
Aug. 14	16.2	1.7	36
Sept. 2	16.3	1.7	45
Sept. 3	Second parathyroid	adenoma removed	
Sept. 4	11.6	2.9	33
Sept. 7	8.6	1.7	38
Sept. 9	12.8	—	—
Sept. 11	11.6	—	—
Sept. 15	10.3	1.5	75
Sept. 23	8.2	1.7	68
Oct. 10	9.1	2.2	30
Oct. 18	9.5	2.0	18
Nov. 5	9.1	2.3	23
Nov. 16	10.0	2.1	33
March 7, 1949	10.5	4.3	15
Feb. 10, 1950	10.4	—	—

Pathology of both tumors—Chief cell adenomata of the parathyroid.

Operated upon: 1st time—July 16th, 1948

2nd time—Sept. 3rd, 1948

inferior thyroid vessels. Before the mass was removed, the right side of the neck was dissected and a normal-appearing parathyroid gland was visualized there. The pathological report on the specimen removed stated that it was a parathyroid adenoma of the chief cell type.

Post-operatively, there was absolutely no change at all in the patient's clinical condition. She still continued to complain of back pain, the urinary Sulkowitch test was still strongly positive, and blood chemistries drawn on July 30th, two weeks after the operation, showed the serum calcium then to be 18.5 mgm per 100 c.c., the phosphorus 1.8 mgm per 100 c.c., and the alkaline phosphatase to have risen to a height of 80 King-Armstrong units (table 1). It was clear that another parathyroid adenoma was still present, and producing the above changes.

On July 29th, during the night, the patient disobeyed strict medical orders by leaving her bed and walking down the corridor of the ward. While returning to her bed, she had a syncopal attack and fell to the floor, fracturing her left hip. X-ray examination revealed a subcapital fracture of the neck of the left femur, with a moderately severe coxa vara deformity and about 2 cm separation of the fragments (fig. 1<sup>a</sup>).

This, of course, complicated the therapeutic problem. It was considered inadvisable to explore the remaining parathyroids until 4-6 weeks time had elapsed from the first operation. By that time the inflammatory reaction would have subsided sufficiently so that an adequate procedure could be performed. At the same time, she had suffered an extremely serious hip fracture which, even in patients without any metabolic bone disease, frequently does not unite properly. It was considered by the orthopedists as most unlikely that the fracture would ever heal as long as there was no active surgical treatment of the fracture (internal fixation). However, because of her poor general condition, the medical service was extremely loathe to subject this patient to any type of operative intervention other than the intended re-exploration of the parathyroids. After much debate and discussion, it was finally decided to treat the fracture simply by traction and immobilization in bed, and then after six weeks had elapsed, have her operated on in an endeavor to halt the hyperparathyroidism.

This was done, and on September 3rd, she went up to the operating room for the second time. After the thyroid lobes were exposed, a tumefaction lateral to and behind the esophagus on the right side was immediately seen. With a little more dissection, a large parathyroid adenoma, measuring  $2\frac{1}{2} \times 1$  inches was revealed, and this was easily removed.

Post-operatively, her course was relatively uneventful. Aside from a few tremors of the face and mouth, and a fleetingly positive Chvostek sign, both of which were easily controlled by intravenous calcium gluconate, there were no major signs of tetany. She was given dihydrotachysterol (hytakerol) but only for a few days, and then this too was discontinued. The second parathyroid adenoma was of the same pathological type as the first, a chief cell adenoma. The serum calcium fell to its lowest level, 8.6 mgm per 100 c.c., 4 days after the operation, but after that time, it rose to normal values, and remained there subsequently (table 1). In addition, there was a slow but steady downward trend in the values of the alkaline phosphatase of the serum. Subjectively, the patient felt markedly improved after the operation, stating that for the first time in years, she was not constantly tormented with bone pains. She still had some pain in her left hip, but this was regarded as being due to the fracture.

Since, in the time interval that had elapsed from the time of the fracture to the time of operation, no significant displacement of the fracture fragments had occurred, it was decided to continue treating her simply with Buck's extension and skin traction, and three months after the occurrence of the fracture, to begin mobilizing her. This was done without incident, and the patient was subsequently discharged to a convalescent home.

Since discharge, she has been in the follow-up clinic several times, the most recent instance being May of 1950. The only complaints she now has are of mild, generalized, mainly arthritic pains in the shoulders, elbows, wrists, and left hip. She is able to walk without assistance, although she does carry a cane. Serum calcium and phosphorus and alkaline phosphatase determinations are all normal at the present time (table I). X-rays of the entire skeletal system have demonstrated a remarkable healing of the bone lesions noted previously. The cystic areas have been filled in, the density of the bone is much heavier now than it was formerly, so that it now seems normal, and there has been a reconstitution of the normal cortical structure of the bones (figs. 1<sup>b</sup>, 2<sup>b</sup> and 3<sup>b</sup>). The subcapital femur fracture has healed.

#### DISCUSSION

It is now generally recognized that at least in this part of the World hyperparathyroidism often leads to nephrolithiasis long before skeletal signs develop.

Thus, in each patient with renal stones but certainly in patients with recurrent renal stones, careful investigation for the presence of signs of hyperparathyroidism is necessary. The patient reported here underwent a left-sided nephrectomy for calculous pyelonephritis in 1943. She developed a right-sided pyelonephritis due to another renal calculus in 1946. She thereafter suffered from unexplained severe pains in the back resembling a sciatic syndrome due to a herniated intervertebral disc. Two myelograms were negative. During this period x-rays of chest, skull, spine, pelvis and abdomen were made repeatedly and showed a completely normal bone structure. This evidently was the reason why the possibility of hyperparathyroidism was not considered and why no determinations of the calcium, and inorganic phosphorus of the serum were made, and why no calcium balance studies were done. The alkaline phosphatase of the serum was determined and found to be hardly increased. This in itself is good evidence that at that time the bone lesions could not have been extensive although the hyperparathyroidism had already led to recurrent renal stones and bone pain. In 1948 new roentgenograms showed the presence of bone lesions which favored the diagnosis of hyperparathyroidism. Careful biochemical investigation did not reveal all the signs which are characteristic of hyperparathyroidism. It is true that the serum calcium (16.4 and 17 mg.%) and the alkaline phosphatase of the serum (57 and 72 King-Armstrong units per 100 c.c.) were very high. On the other hand, there was no decrease of the inorganic phosphorus of the serum, and balance studies of the urinary excretion of calcium showed only a high normal excretion of calcium without the excessive hypercalciuria usually present in hyperparathyroidism. Notwithstanding the two latter negative findings, history, x-ray picture of the bones, and increase of serum calcium and alkaline phosphatase were sufficient evidence for the diagnosis of hyperparathyroidism.

Whereas by far in the greater part of the cases of hyperparathyroidism only one hyperfunctioning parathyroid adenoma is present, this patient belongs to the 15 per cent of the cases where two or more adenomas are present. At the first operation only one adenoma was discovered and removed. Consequently, the hypercalcemia was not modified by the operation. As a matter of fact, after the intervention, the serum calcium rose to 18.5 mg.% and the alkaline phosphatase to 80 King-Armstrong units per 100 c.c. of serum. At this time, the inorganic phosphorus of the serum also appeared to be decreased (1.8 mg.%). Six weeks later, when the second adenoma was removed, the serum calcium fell within 4 days to 8.6 mg.%, the inorganic serum phosphorus rose gradually, and the alkaline phosphatase of the serum decreased until normal levels were reached (table I).

Between the two operations, the patient suffered a pathological subcapital fracture of the left femoral neck (fig. 1<sup>a</sup>). There was so much separation between the fracture segments of the femur and the position was so unfavorable, in any other patient surgical internal fixation with screw bolts would have been the treatment of choice. In this patient, the marked degree demineralization of the fracture fragments due to fibrous osteitis seemed to militate against this approach. The fracture was therefore treated by simple traction.



The rapid recovery of this patient after the second operation is remarkable. The cystic areas present in different bones filled in, the density of the bones became much heavier than it was formerly, and reconstitution of the normal cortical structures of the bones have taken place (figs. 1<sup>b</sup>, 2<sup>b</sup> and 3<sup>b</sup>). In addition, to everybody's pleasant surprise, the subcapital fracture of the left femur has healed (fig. 1<sup>b</sup>). The active regeneration of bone which follows the removal of parathyroid adenomas has evidently been sufficient to overcome the separation of the bone fragments and to fill the intervening space between the fragments. Now, two years after operation, the patient is able to walk with a slight limp and with the use of a cane.

#### SUMMARY

A patient with hyperparathyroidism is reported in whom the disease gave rise to the following signs:

1. Left-sided calculous pyelonephritis necessitating nephrectomy in 1943.
2. Right-sided pyelonephritis due to a ureteral calculus in 1946.
3. Severe bone pains and a sciatic syndrome which gave the impression of being due to a herniated intervertebral disc. Roentgenological examination of the skeleton at that time did not raise the suspicion of hyperparathyroidism. Two consecutive myelograms were apparently normal.
4. In 1948 new roentgenograms revealed bone changes indicating the presence of hyperparathyroidism. Only then an increase of the serum calcium and of the alkaline phosphatase of the serum were found.
5. At the first operation one parathyroid adenoma was removed. Since the biochemical syndrome did not improve the patient was re-operated. After a second parathyroid adenoma had been found and removed, a complete clinical cure set in.
6. Between the two operations the patient suffered a pathological subcapital fracture of the left femoral neck. This fracture healed under simple traction during the period of bone regeneration which followed the removal of the two parathyroid adenomas.

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## BLOOD IODINE AND I-131 EXCRETION IN DIAGNOSTIC PROBLEMS OF HYPERTHYROIDISM\*

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Classical descriptions of the disorder we now recognize as hyperthyroidism were made as early as 1825 by Caleb Hillier Parry (1), a physician at Bath, in 1835 by Robert Graves (2) of Dublin and in 1840 by Carl von Basedow (3) of Merseburg. There is no doubt that both Parry and Graves clearly delineated the syndrome, but the name of Basedow has dominated descriptions of the disease originating on the Continent while Graves' name has been more commonly applied by English and American authors. The valiant efforts by Osler to re-establish Parry in his historical primacy have never had much support. To the three classical symptoms of the disease, exophthalmus, goiter and tachycardia, known as the "Merseburg Triad", Pierre Marie (4), in 1883, added the characteristic fine, rapid tremor. The next addition to the diagnostic features of this disorder was made by Adolph Magnus-Levy (5) in 1895, when he showed that the oxygen consumption was distinctly increased. After that time, the clinician had exophthalmus, goiter, tachycardia, tremor, and increased basal metabolic rate as features in the diagnosis of the hyperthyroid state.

It might seem that with such prominent clinical features there would be only rare difficulty in arriving at a clinical diagnosis and yet we know there is no easy unanimity of opinion regarding many of the patients suspected of this disorder. When we consider that a palpable goiter can be absent and that diagnostic eye signs are not infrequently missing, we become more aware of diagnostic difficulties. Trousseau (6), as early as 1862, pointed out this problem and used the term "formes frustes" to indicate those patients in whom some or all of the cardinal symptoms of the disease were absent. When we realize that many of the symptoms and signs of Graves' disease are merely manifestations of a hyperkinetic state and that not all hyperkinetic states are due to thyroid hyperfunction, we realize how difficult the situation may become.

The search, therefore, has continued for purely objective methods of establishing or confirming the diagnosis of Graves' disease. Of these methods, the first was the determination of the basal metabolic rate. Useful as this method has been, it is by no means an ideal solution. It is generally recognized that rather severe and obvious hyperthyroidism can exist with only minor elevations of the basal rate. In addition, this determination requires the cooperation of the patient and in some instances a satisfactory reading cannot be obtained no matter how much effort is made by the subject or the physician. As a further complication we have recently shown (7) that there is a whole series of medical disorders in which the basal metabolic rate is elevated, but where there is no valid reason to suspect thyroid hyperfunction. It is obvious then, that the determination of

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the basal metabolic rate cannot answer our problem of a purely objective method for the diagnosis of Graves' disease.

An additional contribution to this problem came from our own hospital in 1922 when A. A. Epstein and H. Lande (8) pointed out for the first time that there was a reciprocal relationship between the level of the blood cholesterol and the degree of thyroid function. They showed that in hypothyroid states the serum cholesterol tended to be elevated above the normal while in hyperthyroid conditions the cholesterol was either normal or low. These observations have been amply confirmed and in every large series of cases have proved to be true. So far as the clinician is concerned, however, the value of these conclusions is reduced when he is faced with a single case. The most that can be said is that a distinctly high cholesterol value makes the diagnosis of Graves' disease less likely but it does not exclude it. A low cholesterol level, on the other hand, has very little additional diagnostic value.

So the search has gone on for other laboratory procedures of diagnostic value. This paper concerns itself with two of these; namely, the level of the protein-bound iodine of the plasma and the urinary excretion of tracer doses of radioactive iodine after oral administration.

#### SELECTION OF MATERIAL

All patients who had the level of the protein-bound iodine of the plasma determined were included in this study. For the most part, these represented some diagnostic difficulties with regard to their thyroid status. The usual procedure had been to study excretion with I-131 first because this is a much simpler and quicker determination than the blood iodine test. In general, when the tracer studies and the clinical picture were in clear agreement no blood iodine values were requested. This method of approach obviously results in a non-representative series so far as the data presented in this report are concerned. It was only in those cases in which the clinician was not sure of the diagnosis *after* the I-131 tracer studies were completed that blood iodine studies were performed. This group of 164 cases, therefore, represents a selected series of diagnostic problems so far as the presence or absence of hyperthyroidism is concerned and does not represent a cross-section of all the material seen in the hospital during the period of this study.

#### BASIS FOR FINAL DIAGNOSIS

In order to evaluate any diagnostic procedure it is necessary to know how accurately it predicts the correct diagnosis. In certain diseases this diagnosis can be determined with unquestioned accuracy in almost every instance. In Graves' disease, however, the situation is not so clear and there will be cases in which no unanimity of opinion will be reached even after the most exhaustive investigation. For this study, we have excluded all cases in which there was not general concurrence in the diagnosis of either hyperthyroidism or euthyroidism by all the observers responsible for the care of the patient. In ward patients the final discharge diagnosis was accepted. In private cases the physician in charge re-

corded the diagnosis on the basis of all the data made available to him, clinical and laboratory. Wherever no definite decision could be reached the case was excluded from the series.

#### METHODS

The protein-bound plasma iodine was determined after dialysis by the method previously described from this laboratory (9).

The excretion of I-131 was determined in the urine passed in a 24 hour period

TABLE I

*The level of the protein-bound plasma iodine expressed in micrograms per 100 cc. and the excretion of I-131 expressed in per cent of the administered dose in cases of euthyroidism*

CASE NUMBER	BLOOD IODINE	I-131 EXCRE- TION	CASE NUMBER	BLOOD IODINE	I-131 EXCRE- TION	CASE NUMBER	BLOOD IODINE	I-131 EXCRE- TION	CASE NUMBER	BLOOD IODINE	I-131 EXCRETION
1	6.6	—	23	6.0	24	45	7.3	36	67	8.1	55
2	7.0	—	24	4.9	34	46	5.4	35	68	8.3	50
3	7.0	—	25	6.0	34	47	7.7	13	69	7.7	14
4	7.6	—	26	7.3	11	48	7.2	32	70	6.8	14
5	9.7	44	27	7.0	41	49	7.0	—	71	7.1	26
6	10.8	31	28	6.8	40	50	6.4	—	72	6.6	22
7	7.0	48	29	6.7	27	51	6.2	34	73	7.0	51
8	9.8	—	30	7.2	22	52	5.9	18	74	8.0	44
9	8.2	—	31	5.3	36	53	7.0	41	75	9.5	—
10	9.2	38	32	6.4	7	54	7.2	38	76	6.6	40
11	8.8	—	33	6.6	36	55	7.9	56	77	7.4	24
12	8.5	—	34	6.7	31	56	6.1	—	78	6.6	34
13	6.6	—	35	7.8	55	57	4.5	54	79	7.2	13
14	7.6	52	36	8.3	42	58	5.8	10	80	6.4	47
15	8.5	27	37	8.2	50	59	7.8	13	81	8.6	38
16	7.3	16	38	7.3	41	60	5.4	45	82	7.5	40
17	6.7	52	39	7.4	—	61	6.8	30	83	7.9	47
18	9.0	22	40	6.4	24	62	8.3	29	84	6.8	24
19	5.6	26	41	5.0	—	63	11.3	18	85	9.5	53
20	7.2	46	42	6.2	35	64	7.1	44			
21	6.8	17	43	6.2	26	65	7.7	50	Mean.	7.3	32.8
22	7.2	8	44	7.4	16	66	7.5	40	S. D.	±1.4	±13.9

after the oral administration of a tracer dose of 100 microcuries of I-131 without carrier iodine.<sup>1</sup>

Because it has been demonstrated (10) that the administration of organically bound iodine compounds such as thyroid extract, gall bladder dye, dyes for intravenous pyelography, lipiodol, and other related compounds affects the value of the protein-bound iodine as determined by present procedures, all patients who had received these substances were excluded from this series. It is also known that the administration of iodine, thyroid extract and drugs of the thiouracil series disturbs the excretion of I-131. Patients known to have been exposed to

<sup>1</sup> The I-131 was supplied on allocation by the United States Atomic Energy Commission.



these drugs were excluded. Severe renal disease and marked oliguria impair the value of tracer studies and no patients with these disorders were included.

### RESULTS

It was found that 164 patients were available for these studies. Of these the final diagnosis in 79 was hyperthyroidism and in the remaining 85, the diagnosis of euthyroidism was reached. All these patients had blood iodine determinations recorded. Of the 79 hyperthyroids we had available excretion studies of I-131 in 71. Of the 85 euthyroid patients such data were available in 69.

TABLE II

*Data similar to that in TABLE I in cases of hyperthyroidism*

CASE NUMBER	BLOOD IODINE	I-131 EXCRE- TION	CASE NUMBER	BLOOD IODINE	I-131 EXCRE- TION	CASE NUMBER	BLOOD IODINE	I-131 EXCRE- TION	CASE NUMBER	BLOOD IODINE	I-131 EXCRETION
1	8.1	—	22	12.3	17	42	15.4	25	62	10.6	55
2	25.2	2	23	15.8	39	43	10.0	1	63	11.7	18
3	13.6	—	24	8.1	41	44	11.5	21	64	18.5	24
4	15.6	5	25	18.0	12	45	23.1	1	65	13.3	13
5	12.9	7	26	19.8	25	46	12.7	7	66	10.8	50
6	19.6	4	27	12.5	12	47	10.1	30	67	10.9	34
7	10.0	25	28	18.8	2	48	16.3	33	68	19.8	25
8	15.1	11	29	12.7	25	49	11.3	16	69	13.4	6
9	13.5	11	30	13.2	55	50	11.3	16	70	12.5	17
10	11.7	16	31	16.4	4	51	7.0	17	71	8.5	21
11	16.8	2	32	14.8	3	52	13.2	19	72	14.6	17
12	9.3	10	33	10.0	6	53	11.9	21	73	11.7	33
13	10.0	23	34	12.3	—	54	11.3	24	74	—	14
14	11.4	44	35	12.3	38	55	11.8	19	75	13.4	35
15	12.5	9	36	11.4	32	56	15.9	68	76	15.5	8
16	10.2	10	37	10.7	24	57	11.8	25	77	7.9	32
17	9.1	3	38	14.2	27	58	10.4	33	78	9.5	24
18	7.4	23	39	22.2	6	59	11.6	51	79	10.9	56
19	11.5	23	40	9.2	18	60	6.6	26			
20	10.5	12	41	14.6	21	61	9.4	18	Mean...	12.9	21.2
21	9.8	25							S. D....	+3.8	±14.6

An analysis of the data shows that the mean values and standard deviations were as follows:

Euthyroid Patients	Blood Iodine	$7.3 \pm 1.4$	gamma per cent
Euthyroid Patients	I-131 Excretion	$32.8 \pm 13.9$	per cent
Hyperthyroid Patients	Blood Iodine	$12.9 \pm 3.8$	gamma per cent
Hyperthyroid Patients	I-131 Excretion	$21.2 \pm 14.6$	per cent

These figures leave no doubt that in this series of cases the determination of the protein-bound iodine of the blood is a more accurate method of establishing the diagnosis of hyperthyroidism than is the urinary excretion of radioactive iodine. In fact, the significance ratio is about three to one in favor of the blood iodine determination.

If we accept 8.0 micrograms per cent and I-131 excretions of 25 per cent as the dividing points between euthyroidism and hyperthyroidism then we find that fifteen normals were above 8.0 (average 9.2). Of these, seven had I-131 excretion above 25 per cent. There were four hyperthyroids with blood iodines below 8.0 (average 7.2). Of these, two had I-131 excretions below 25 per cent.

There were twenty-one normals with I-131 excretions below 25 per cent (average 17). Of these, nineteen had blood iodine values below 8.0. There were twenty cases of hyperthyroidism with excretions above 25 per cent (average 41). Of these, eighteen had blood iodines above 8.0.

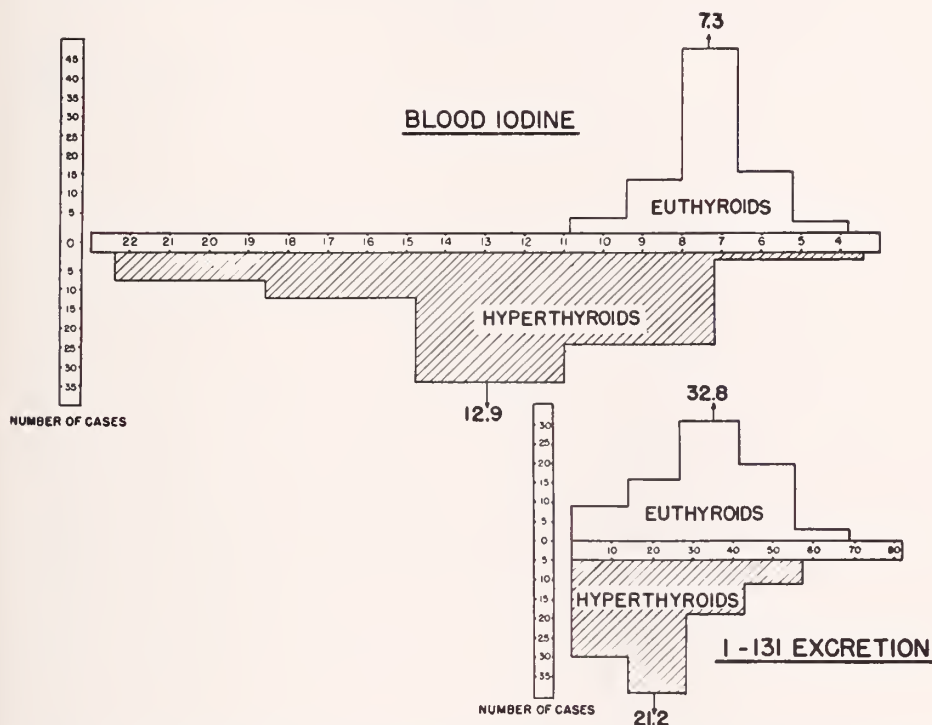


FIG. 1. The distribution of the cases of euthyroidism and hyperthyroidism plotted according to the blood iodine levels and the excretion of I-131. Each horizontal division represents one standard deviation on the corresponding scale.

#### SUMMARY

A study of 85 cases of euthyroidism and 79 cases of hyperthyroidism which originally offered diagnostic difficulties to the clinician and in which the I-131 excretion did not establish the diagnosis is presented. These cases were then studied as to the level of the protein-bound iodine of the plasma. The final diagnosis was unequivocal in all instances. Review of the data using standard statistical procedures shows that the level of the protein-bound iodine of the plasma is about three times as significant as the radioactive iodine excretion in establishing a correct diagnosis. How these results would be affected if an unselected series of cases were studied cannot be stated from this investigation.

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# THE SIMULTANEOUS OCCURRENCE OF ACTIVE PEPTIC ULCER AND ACTIVE HYPERTHYROIDISM

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The occurrence of active peptic ulcer and active hyperthyroidism in patients at the same time seems logical. They both are psychosomatic diseases; they usually elect young adult life; they tend to chronicity and relapse; they both are often associated with stress, striving, worry, anxiety, etc.; they both are helped by rest, medication, re-education or psychotherapy and surgery; a like controversy as to the relative value of medical treatment and surgery exists in both. There is no doubt they have an identical background and Crile very aptly stated "the outstanding difference in these two diseases is that the brother gets the ulcer and the sister gets hyperthyroidism" (1). However, when one analyses these diseases from their relationship to the vegetative nervous system, one sees that they cannot be ascribed to one and the same etiological factor. Since the time of Eppinger and Hess (2) many have adhered to the general conception that the vegetative nervous system is a vastly correlated nervous chain in which the vagus impulses on the one hand are counteracted by the sympathetic impulses on the other; the two behave like the arms of a scale and provide a protective balance in function. If the tone of one goes up and accordingly presents certain symptoms, then the other exhibits clinical manifestations of a relatively lower or actual lower tone. From these studies they advocated the vagotonic and sympathicotonic syndromes. It has been assumed and recent beneficial results from vagotomy have helped the assumption that in peptic ulcer there is a definitely increased chronic excitability of the vagus nervous system; this accounts for the frequent associated findings: slow pulse, contracted pupils, increased salivation, increased gastric secretion, increased gastric acidity, tendency to pyloric spasm, constipation, etc.

In hyperthyroidism on the other hand we have always accepted an increased activity of the sympathetic nervous system to account for the clinical findings of rapid pulse, dilated pupils, diminished gastric secretion, frequently even achylia, tendency to diarrhea, etc. From this reasoning, one should therefore consider the simultaneous occurrence of hyper-excitability of the vagus and sympathetic systems as contradictory.

I have always advocated that this sharp division or mutual antagonistic action should not be accepted as a clear-cut dictum; it is not borne out by accurate studies of nerve distribution and nerve function. One should speak of a disharmony of the vegetative system rather than a strict antagonism. The clinical existence of hyperthyroidism and peptic ulcer speaks against such an absolute demarcation. Patients with both of these diseases evidence some manifestations of a sympathicotonia and some manifestations of a vagotonia at the same time. For example, two of my cases had a comparatively slow pulse rate, at times eighty



to ninety, and a marked gastric hypersecretion and hyperacidity with a basal metabolism of plus forty. Andrews (3) described a case of simultaneous hyperthyroidism and massive hemorrhage from duodenal ulcer (basal metabolism plus twenty) but gastric analysis had shown an achlorhydria. This combination also occurred in one of the cases from the Lenox Hill Hospital records and another was reported by Neidhardt and Blaum (4). Ulcer in the presence of anacidity contradicts the generally accepted principle: "no acid, no ulcer."

In actuality, the simultaneous occurrence of these two diseases is not frequent. At the Lenox Hill Hospital with 12,500 admissions a year, there were only two cases in the last ten years.

From the Cleveland Clinic, Dr. George Crile, Jr. wrote me recently that from the thousands of cases of both peptic ulcer and hyperthyroidism observed at the clinic, the simultaneous occurrence of these two diseases has been very rare; to his knowledge, he has not seen a single instance of both occurring in the same individual.

In the literature, there are many general references to this combination but not many accurate descriptions of cases that had been followed in detail.

Andrews (3) reports a case of simultaneous ulcer and hyperthyroidism. He first performed a gastroenterostomy and cholecystectomy for the bleeding duodenal ulcer; the patient got a marked thyrotoxic crisis; seven weeks later he did a thyroidectomy.

Crile (2) analyzed 9618 patients with hyperthyroidism and peptic ulcer was present in forty-eight cases (1 in 200). He found that the ulcer could be relieved or cured by thyroidectomy but if not, he performed his operation of denervation of the adrenals.

Trice (5) reviewed the charts of 124 cases who were operated upon either for ulcer or hyperthyroidism and noted that the incidence of peptic ulcer in his cases of hyperthyroidism was no higher than the incidence of peptic ulcer in general.

Neidhardt and Blaum (4) studied the histories of thirty-seven patients with marked Basedow disease and three with thyrotoxicosis and found seven cases had duodenal ulcer and one had pyloric ulcer, a rather unusual proportion.

Walinski and Helfors (6) examined 3 patients with peptic ulcer and eight patients with gastritis, for signs of hyperthyroidism. He payed particular attention to repeated basal determinations. He found greatly increased values in 30% of all the cases. He related this unusual high percentage to battle conditions. Only two had small goitres, none had exophthalmus. We must realize that plus basal metabolism does not necessarily mean the clinical picture of hyperthyroidism or particularly exophthalmic goitre. He mentions only six patients with distinct signs of both hyperthyroidism and ulcer who were resistant to therapy. No details were cited about any of the cases, as he seemed mostly interested in the question of gastric secretion in hyperthyroidism a frequently discussed problem. (Lewit (7); Lockwood (8); Trice (5); Brown, Pendergrass and Burdick (9)).

Robinson (10) describes the very unusual occurrence of both duodenal ulcer and hyperthyroidism in each of female twins, age forty-two, (in one the basal

metabolism was plus 35, in the other plus 63.) The duodenal ulcer was relieved by diet and alkalis and the hyperthyroidism subsided without treatment.

During the last ten years, I have had four proven cases from my own private practice.

#### CASE REPORTS

*Case 1. History.* Mrs. I. W., aged 34, housewife, married, two children was seen by me on October 14, 1940.

She had no serious illnesses and no operations. Menstruation regular. Eight years previously she began to have gastric symptoms of belching, vomiting, and pain relieved by antacids or by taking foods. Never required any hypodermic medication. Had these recurrent attacks of gastric discomforts at intervals over the many years. In January, 1940, she became very nervous and had marked palpitation. She went to the Mount Sinai Hospital and there the basal metabolism tests varied between plus 39 and plus 51. She was given Lugol's iodine solution with marked temporary benefit.

When seen by me in October of 1940, she again had the same gastric discomforts, pain, vomiting and belching; she had a marked tremor of the hands; was extremely nervous; eyes were slightly prominent with a mild Stellwag sign; pulse, 120; blood pressure, 120 systolic and 80 diastolic; temperature, normal. The thyroid gland was definitely prominent and firm. X-ray examination of the gall bladder was normal; and that of the gastro-intestinal tract showed a constant deformity of the first portion of the duodenum characteristic of duodenal ulcer. Gastric analysis showed free HCl 92, total acidity 110, but no gastric hypersecretion. A blood count showed a relative lymphocytosis; (hemoglobin, 94%; red blood cells, 4,500,000; white blood cells 8,000 (polys 55%, lymphocytes 42%, monos 3%). The urine was normal. Basal metabolism, plus 49. The patient was put to bed and placed on a strict dietetic (11) and medicinal ulcer regime. In addition she was given Lugol's iodine solution. Her gastric discomforts improved so much right away that she would not consider any further treatment for her thyroid. However, her nervousness kept up; her basal metabolisms remained high (October 25, 1941 plus 69—December 20, 1941 plus 69). She re-entered the hospital in February, 1942. At this time her stomach disturbance was entirely relieved; but she was extremely nervous and her eyes had become more prominent. She was carefully prepared with Lugol's solution of iodine and sedatives, and on March 9, 1942 a sub-total thyroidectomy was performed by Doctor Stetten. The operation was well tolerated and she made an uneventful recovery. She has been perfectly well since (up to time of writing). Her pulse is 72, her basal metabolism is plus 4, she conducts herself as a perfectly normal person.

*Case 2. History.* Mr. L. B., a musician, aged 31, was seen by me for the first time on January 21, 1942. Five years previously complained of pains in the stomach, and an x-ray showed an active duodenal ulcer (Doctor I. Held). He improved under diet and medication but had a recurrence of symptoms three years afterwards, when x-ray again showed extensive duodenal ulceration; again he was relieved by medication and diet. When he came to me, he was complaining of the classical symptoms of peptic ulcer. X-ray showed extensive deformity on the lesser curvature of the cap with the presence of a crater.

*Examination.* He showed typical symptoms of thyrotoxicosis—extremely nervous and restless, tossing around in bed, marked exophthalmus with Stellwag's and Von Graefe's signs, and a severe tremor. The thyroid was prominent and firm. Temperature, 99.4°F. Pulse varied from 84 to 124 and showed marked irregularity. The electrocardiogram demonstrated auricular fibrillation. The basal metabolism rate was plus 70. He was too restless for a gastric analysis. His urine was normal. His blood count showed no anemia, but repeatedly a lymphocytosis; hemoglobin, 89%; red blood cells, 5,300,000; white blood cells, 5,900 (polys, 48%; lymphocytes, 44%; monos, 3%; transitionals, 3%; eosinophiles, 1%).

He was placed on my strict dietetic and medicinal ulcer regime and in addition was given Lugol's iodine solution. His gastric symptoms began to clear up immediately but his hyper-

thyroid discomforts, restlessness, sleeplessness, nervousness, extremely severe heart palpitation persisted. Digitalis was pushed to the point of tolerance and then quinidine was added in large doses but fibrillation could not be reverted to normal sinus rhythm. The latter was so severe that he was willing to undergo an operation. After proper preparation by rest in bed, iodine and sedatives, the basal metabolism rate gradually came down to plus 27 but stayed there. On June 29, 1942, six months after the initiation of treatment, a subtotal thyroidectomy was performed by Doctor Stetten, (pathological report hyperplastic thyroid). He made an uneventful surgical recovery. His gastric symptoms were all gone; his hyperthyroid symptoms were greatly reduced; he regained his weight and was able to assume his activities as a violinist in an orchestra. However, the auricular fibrillation, although slow, persisted and his exophthalmos remained the same. The basal metabolism rate also remained high, varying from plus 29 to plus 60; his cholesterol was 150 mg. He showed a persistent leucopenia with a relative lymphocytosis: hemoglobin, 89%; Red Blood Cells, 4,600,000; White Blood Cells, 6,200 (polys, 50%; lymphocytes 50%). The urine examinations were repeatedly negative.

He soon had to stop work again because of thyrotoxic symptoms, although no gastric symptoms returned. Thiouracil was just then being introduced and he began to take it in September, 1943. He was started on 0.8 Gm. He immediately reacted well: he gained more in weight, his nervousness decreased, his palpitation diminished, his eyes were less prominent, the basal metabolism rate gradually came down from plus 40 to plus 32, plus 29, plus 18, plus 10, minus 5 in April, 1944, and plus 3 in June, 1946. His auricular fibrillation however persisted. On careful experimentation we found that his daily maintenance dose of thiouracil was 0.2-0.4 gm. He returned to work, felt fine and was very happy. On October 26, 1944, after one year of constant thiouracil administration without any toxic effects, he suddenly developed symptoms of agranulocytosis: sore throat, rash, high temperature, a white blood cell count of 700 (polys, 3% lymphocytes, 97% red blood cells, 5,000,000; hemoglobin, 93%). The thiouracil was immediately stopped; penicillin injections, liver injections, repeated transfusions were given, and the patient recovered. The thiouracil was not resumed but iodine was given. He felt well for many months but the basal metabolism slowly began to mount again, (January 1945, plus 19, then plus 17, plus 14, plus 13 and in spite of increased doses of iodine, it reached plus 32 in January, 1946). Severe symptoms of thyrotoxicosis recurred but no gastric discomforts. Although we realized the dangers, thiouracil was again started most cautiously and in very small doses, 0.2 gm., with careful check-ups of the blood. He again began to improve and in three weeks the basal metabolism was plus 12. Four days after, agranulocytosis again suddenly developed. This time, however, with anemia: hemoglobin, 80%, red blood count, 3,200,000; white blood cell count of 1,600 (lymphocytes 100%). With this there was a very high temperature and an extensive lobar pneumonia. Cardiac decompensation, and renal insufficiency developed and in spite of all forms of heroic, specific and supportive measures, the patient died.

*Case 3. History.* Dr. J. W., aged 49, a dentist, married, two children, and a heavy smoker. He was seen by me on June 1st, 1949. He had had digestive difficulties because of a duodenal ulcer for over twenty years, with periodic acute attacks every five or six years. During the last three years he has had only short times of freedom from distress, and in the last two months he has been in almost constant pain day and night; he was not relieved by Sippy diet and alkaline powders. He was diagnosed as an intractable ulcer and came to me for consultation to undergo surgery, although he was most unwilling to do so.

*Examination.* He was very nervous and restless and emotionally upset on account of his family. His eyes were prominent with a slight exophthalmus; slight tremor of his hands. Heart rate, 108, blood pressure at first 200 systolic and 110 diastolic, which subsequently came down to 160 systolic and 90 diastolic. There was a definite tenderness over area of the duodenum. All reflexes were exaggerated. No other abnormalities were noted.

*Laboratory tests:* Gastric analysis after an Ewald test meal showed surprisingly low acidity: free hydrochloric acid, 20; total acidity 43, (possible sympathetic influence?). Blood study: hemoglobin, 95%; red blood count, 5,190,000; white blood count, 9,200 (polys 72%, lymphocytes 24%, eosinophiles, 1%). The stool and urine examinations were negative.



An electrocardiogram showed no significant abnormalities. The basal metabolic rate was plus 20 on repeated tests. X-ray examination showed extensive ulceration of the cap with two or three craters.

*Treatment.* On reviewing his former physician's advice, it was found that he never followed out a careful medical treatment; therefore, one more attempt was made with my rigid ulcer regime from a dietetic, medicinal and emotional point of view. He stopped work and stopped smoking completely. He reacted favorably right from the start. In ten days he was free of stomach distress and he was permitted to resume two hours work a day because he was worried about his financial status. In spite of his freedom from gastric discomforts he continued with his tachycardia, circulatory instability and increased basal metabolism. He was started on Probaeil, 300 mgms. a day for one week and this was then reduced to a maintenance dose of 50 to 100 mgms. a day. He is now feeling well but will have to be followed up to see whether conservative medical treatment will suffice, or whether surgery will have to be undertaken for one or the other or both conditions.

*Case 4. History.* Mrs. D. F., aged 41, housewife, married, two children. Smokes one package of cigarettes a day. She was seen by me for the first time on October 27, 1947.

In November, 1946, she had a subtotal gastrectomy performed in Morocco because of periodic attacks of duodenal ulcer over a period of seven years. One brother died of an operation for ulcer, and one sister is being treated for an ulcer. Even before the operation, she noticed being very nervous, but she attributed this to her stomach upsets and her marital disharmonies. In January, 1947 she noticed that she was losing in weight and that her left eye was "more prominent, glistening and protruding." She was very shaky and emotionally upset. She perspired most of the time, got tired very easily and had sensations of gone feelings and dizziness. She ate a general diet without any regular discomforts, but at times she vomited acid and bitter stuff after eating.

*Examination* showed a highly intelligent, nervous, restless and perspiring little person (she weighed 105). Marked tremor of the hands; definite left exophthalmus with positive Stellwag and Von Graefe signs. Both thyroid lobes were very prominent, no bruit. The heart was normal but the rate was 114; blood pressure, 120 systolic and 80 diastolic. The abdomen showed scars from her operation but otherwise negative. All reflexes were exaggerated.

*Laboratory Tests.* Gastric analysis after an Ewald test meal showed hardly any gastric secretion with free hydrochloric acid 0, and total acidity 22. Blood count: hemoglobin, 87%, red blood count, 4,470,000; white blood count, 10,000; (polys 55%, lymphocytes 40%, monos 5%). Examination of stool was negative. The urine examination was also negative except for ten to twelve pus cells per field. The basal metabolic rate was repeated several times and was plus 20. The sedimentation rate was normal. The cholesterol was 181 mg. X-ray examination showed a stomach almost one third its normal size, with a normal functioning stoma.

*Treatment.* She was placed on a technically well prepared general diet and simple psychotherapy was instituted; as for medication, she took butisol sodium, vitamins, and Probaeil, 200 mg. a day for a week and gradually reduced to a daily maintenance dose of 50 mg. Under this combined therapy she began to improve at once. Her discomforts disappeared; she gained in weight; her metabolic rate gradually came down to minus 5, and she was able to undertake a trip out West in June, 1948. In June, 1949, I received this follow-up note: "when first out West she felt so well that she stopped the Probaeil; after a little while all her symptoms recurred; her basal metabolism increased to plus 13, she began taking iodine but this did not give her the relief Probaeil did, and she was being prepared for operation."

#### SUMMARY AND CONCLUSION

1. Patients with both manifestations of active peptic ulcer and Basedow disease occurring simultaneously, are not frequently observed. Their concurrence, however, contradicts the assumption of an ever existing vagus sympathetic



balance. The simultaneous symptoms would point to a simultaneous hyperactivity of both the vagus and sympathetic systems. It is more reasonable to speak of a dysfunction of the vegetative nervous system (Von Bergmann (2)).

2. Four such striking cases were described; one improved without any operation; one had both a subtotal gastrectomy and thyroidectomy; two had thyroidectomies without any gastric surgery.

3. There is no rule to indicate whether medical or surgical therapy should be adopted; it will depend upon the history, the severity and intractability of the clinical symptoms, and the physical condition of the patient. Each of the two disturbances has to be judged individually without necessarily considering any interdependence.

4. The ulcer can be cured medically, even though the symptoms of the thyrotoxicosis persists. If surgery is indicated for both conditions, the thyroid, when possible, should be dealt with first.

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# CHANGING PATTERNS IN THE DEFINITION OF ACUTE LUPUS ERYTHEMATOSUS

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I have chosen as my contribution to this symposium on the basis of disease a discussion of the pathology of acute lupus erythematosus and allied diseases. This selection is justified by the gain in insight which has resulted from recent histo-chemical investigations; and because previous microscopic observations have led to an inquiry into the biology of connective tissue since alterations in the structure of this tissue were found to be conspicuous in this disease. It is by such reciprocal stimulation that basic sciences as well as medical investigations approach the ultimate aim of medicine: to understand the intrinsic reason of disease.

The understanding of a disease is based in large measure upon its definition; but definitions change with successive periods as the evolution of knowledge causes a change in principles underlying definition. Historically, crude clinical symptomatology and the philosophical interpretation of symptoms were the dominant principles of medical thinking until their dethronement by the anatomical doctrine of Morgagni and his followers. This was a great advance with disease being defined in accord with the more objective principle of anatomic alteration. This period of observational pathology culminated in the teachings of Rokitansky and the Vienna School of Medicine. The anatomic definition of disease, however, was still dependent only upon static criteria. The morbid process was merely fastened to the descriptive characteristics of the anatomic alteration. In the meantime the fundamental sciences, physics and chemistry had already advanced beyond the scope of mere observation. The new tactics and strategy of science, in the words of Conant, demanded an explanation of the facts perceived by the senses. As this new spirit entered into the investigations of vital phenomena, it became evident that the exploration of morbid states could be successfully promoted only by an inquiry into their causality. Pathogenesis became the sole and exclusive principle upon which a comprehensive definition of disease could be erected. This principle was to guide medical activity of the future. How scientific medicine has developed under the influence of this idea since the middle of the Nineteenth Century is an interesting and deserving topic but I fear it would take me too far afield, so I shall limit myself to a brief statement as to how the same trend of changing definitions still operates in our investigation of disease and how it has advanced our understanding of the obscure malady under discussion.

A little over seventy-five years ago, to be precise, in 1873, Kaposi defined acute lupus erythematosus as a disease characterized by cutaneous manifestations and by symptoms of serious, often fatal, constitutional afflictions which

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by their acuteness contrasted with the chronicity of the skin disease. Subsequent observers elaborated upon the clinical symptoms and at the turn of the century Jadassohn summarized available observations. He referred to the frequency of symptoms which pointed to involvement of joints, serous and mucous membranes and kidneys. He emphasized the severity of the general constitutional symptoms, such as fever, headache and prostration. Bacteriologic investigations had failed to disclose a specific cause although the tubercle bacillus was often accused. It is evident that Jadassohn's definition of acute lupus erythematosus was based on clinical symptoms. There was a touch reminiscent of a philosophical interpretation in his statement that "all these symptoms impress the observer as if the body is flooded by toxins". The next two decades added some important laboratory observations such as conspicuous leukopenia and thrombocytopenia, the latter accounting for the frequent symptoms of hemorrhagic diathesis. Moreover, the sensitivity of the patients to sunlight was discovered and the peculiar prevalence of the disease among females became evident.

Anatomic investigations, including histologic examination of the skin had not added criteria for a more objective definition than one based on clinical symptoms. Libman and Sacks described in 1924 a peculiar form of endocarditis in patients who had had the symptom complex of acute lupus erythematosus. Although these authors were not willing to make the diagnosis acute lupus erythematosus, it can be said retrospectively that their gross and microscopic observations constitute the first significant contributions to the pathologic anatomic picture of the disease. The cardiac alterations were analyzed in greater detail by Gross in 1932 and 1940. He added significant microscopic criteria to the anatomic definition of acute lupus erythematosus. To these I shall return shortly. Baehr, Schifrin and I reported in 1935 on conspicuous alterations of blood vessels, especially of glomerular capillaries, supplying further criteria to the anatomic definition. These vascular lesions seem to account for some of the clinical manifestations of the disease, such as hematuria, mucosal ulcerations and even the cutaneous rash, especially in its purpuric forms. Up to this time no correlation could be found between the frequent involvement of serous membranes and joints and the conspicuous vascular alterations. In attempting to explain this coincidence of endocardial, vascular, serosal and joint lesions, we pointed to the fact that all these sites are covered by endothelium and we made the assumption that an endothelio-tropic noxa in a broad sense might be held responsible for these widespread changes. In the light of later observations this hypothesis may be regarded as a speculative interpretation rather than a pathogenetic definition. Our objective observations were confirmed by some authors (Jarcho, Denzer and Blumenthal), while others dissented both in regard to their frequency as well as to their specificity. As we continued our anatomic investigations of acute lupus erythematosus, observation of new cases and the reexamination of old material disclosed microscopic lesions which had escaped our attention in the preceding period. Pollack, Baehr and I reported in 1941 on the occurrence of widespread alterations in connective tissue in acute lupus erythematosus. These were found in all the layers of the heart, in serous mem-

branes, joints and dispersed in mediastinum and retroperitoneal space. The vascular lesions reported previously proved to be the result of alteration of the connective tissue framework of the vessels. These changes centered upon the extracellular portions of the connective tissue, the collagen fibers showing the characteristic structural and tinctorial features of so-called fibrinoid degeneration, while the intermediate ground-substance—which is scarcely visible in normal tissues—became very conspicuous. In subsequent investigations it was shown that the ground-substance showed a considerable degree of metachromasia when stained with toluidine blue, indicating the presence of mucopolysaccharides. An equally conspicuous alteration was found in the spleen where the periarterial zones were markedly widened by the presence of strikingly stout collagen fibers. From these newer observations we concluded that acute lupus erythematosus was defined anatomically by diffuse alterations of the extracellular components of the connective tissue.

Systemic lesions of the connective tissue are not confined to acute lupus erythematosus. In acute rheumatic fever the collagenous tissue of the heart, joints, blood vessels and not infrequently of other sites is electively affected and the collagen fibers also show fibrinoid degeneration associated with mucinous swelling of the ground-substance (Klinge). The widespread vascular necrosis in polyarteritis nodosa has been traced to an initial phase of fibrinoid degeneration; extravascular foci of collagen alteration have been observed not infrequently (Churg and Strauss). But the conspicuous and specific cellular proliferation around the foci of fibrillar alteration points to a difference in nature of these anatomical symptoms of the morbid process to that of acute lupus erythematosus. Diffuse scleroderma shares with acute lupus erythematosus in the localization of the anatomic signs of the disease. Even the nature of the connective tissue alteration seems to be related, although in scleroderma sclerosis of the collagenous fibers over-shadows fibrinoid alteration, while the reverse holds true for acute lupus erythematosus. Yet, the two maladies differ so widely in their clinical symptoms that it seems inadvisable to correlate them because of a similarity of structural change. The last malady which deserves mention is dermatomyositis, because of clinical similarities with acute lupus erythematosus, as well as diffuse scleroderma and the occurrence of vascular necrosis in the organs.

Two generalizations have been drawn from the morphologic observations in these diseases. A common denominator seems to exist in the localization of anatomic lesions in the connective tissue and the conspicuous alterations of the collagenous fibers. Because of the identical composition of this tissue wherever present in the human body, Pollack, Bachr and I believed it warranted consideration as an organic system. This organ concept seemed to be supported by a consideration of the function of the connective tissue. It is not limited to mechanical support of the body and its constituent organs but serves obviously in the maintenance of water metabolism, acid-base equilibrium (Schade) and as a conveyor of metabolites from the blood to the surrounding cells and in the reverse direction. The presence of generalized alterations of this organoid connective tissue system in the maladies just mentioned seemed a warrant for plac-



ing them all in one group. Because the extracellular portions of the connective tissues—especially the fibers—were conspicuously affected, I used the term—diseases of the collagen system.

I now believe, that this term was ill-chosen for two reasons. First, it was not exact because it did not clearly point to the co-existing alteration of the intermediate ground-substance. Second, it was bound to be misunderstood and mistakenly used as a diagnostic term. This was never intended. We wanted to use the term collagen disease only as anatomic delineation of maladies characterized by structural changes of the connective tissue specifically of its extracellular components. In this sense the concept merely gave a descriptive definition in anatomic terms. Since so little was known about the factors which influence the structure and constitution of the connective tissue we believed that investigations of this neglected tissue would be stimulated by calling attention to its morbid states. We hoped that the information and insight thus acquired could then be utilized for a pathogenetic definition of the members of the entire group. This general aim seemed particularly necessary because a premature generalization had been drawn from the objective observations of morbid anatomy. The conspicuous fibrinoid alteration of the connective tissue had been singled out for pathogenetic interpretation. Since experimental observations and clinico-pathologic correlations had established that states of allergy are frequently associated with fibrinoid alteration of collagen it was sweepingly deduced that all morbid states characterized by such connective tissue changes are presumably of allergic background. We had been aware of the relationship between fibrinoid collagen alteration and local tissue hypersensitivity. We were reluctant to invoke this pathogenetic principle for the explanation of tissue changes in acute lupus erythematosus or diffuse scleroderma. Our reluctance was based on the following considerations: first, clinical investigations including the blood picture did not point to the existence of allergy in our patients. Second, fibrinoid collagen changes while undoubtedly present in experimental allergy, also occur in situations in which hypersensitivity can definitely be ruled out. Thus, fibrinoid changes have been reported by Schlossnig in infections with pyogenic organisms and by others in the blood vessels of animals with experimental hypertension. Similar changes can be observed in the base of peptic ulcers of the alimentary tract and in the vicinity of pancreatic necrosis, and finally fibrinoid changes have been produced by trivial mechanical injury in animals. Third, in the connective tissue alterations of lupus as well as scleroderma fibrinoid collagen changes are not the only significant features. The conspicuous swelling and metachromasia of the ground-substance and the sclerosis of the collagen fibers are not correlates of tissue hypersensitivity. These were the main reasons why allergy seemed inadequate to account for the tissue lesions in acute lupus erythematosus and generalized scleroderma. These reasons, however, posed questions which could not be answered by our present information regarding the normal and pathobiology of the connective tissue. Further inquiry was necessary before we could attempt to give a pathogenetic definition of these puzzling diseases.

Limitations of time make it impossible to give an account of our recent in-

vestigations; instead I shall offer a brief summary of their aims. At present we are studying the hormonal factors which control the deposition of the homogeneous ground-substance, its relationship to collagen fibers and the nature of fibrinoid collagen alteration. These studies have not yet reached a conclusion. Indeed they might even lead us far afield.

At the same time morphologic investigations were continued in the hope that new cases might reveal additional criteria for the anatomic definition of acute lupus erythematosus. In the past two years we encountered four cases which showed certain microscopic features in so striking a distribution that their significance was evident and led to the reexamination of our previous material. Gross had already reported identical features in the cardiac vegetations of acute lupus erythematosus and had considered them as pathognomonic for the disease. Ginzler and Fox had seen similar lesions in lymph nodes and kidneys of one case and Pollack, Baehr and I had also recorded them in the kidneys of our twenty cases of acute lupus erythematosus. A detailed description of these microscopic findings can be omitted since a full record can be found in recent publications. In brief, it can be stated that in 41 of 45 cases characteristic hematoxylin stained bodies were found. They were present at times in two or more sites such as heart, lymph nodes, kidneys and other organs, but were always limited to tissues of mesenchymal derivation. Microscopic analysis proved that these hematoxylin stained bodies originated in an alteration of nuclei and that cells involved were exclusively of mesenchymal origin such as fibroblasts, histiocytes, endothelial cells, lymphocytes and polymorphonuclear leucocytes. The frequent occurrence of the lesions in acute lupus erythematosus and their constant absence in control cases permits one to regard them as valid criteria for the anatomic definition of the disease. Yet this descriptive characterization does not add to our information regarding pathogenesis. But cytochemical analysis carried out in collaboration with Drs. Pollister and Leuchtenberger of Columbia University revealed that the characteristic hematoxylin bodies contained partially depolymerized desoxyribose nucleic acid.

This disclosure is of pathogenetic significance because it permits the conclusion that depolymerization of the nuclear chromatin of mesenchymal cells is one of the factors of the morbid process of acute lupus erythematosus. Certainly this information does not yet provide a full pathogenetic definition of the disease because the complicated metabolism of desoxyribose nucleic acid is still far from being understood. The factors which may be responsible for the disturbance of the finely adjusted equilibrium between depolymerase and its inhibitor, (Chargaff and Zamenof) or for potentiation of the depolymerase are still entirely unknown. But Anatomic Pathology has laid the foundation and now invites Physiology and Chemistry to complete the work.

#### SUMMARY

1. Acute lupus erythematosus was primarily defined by clinical symptoms only, which never could lead to a pathogenetic definition.
2. The first anatomic criteria of acute lupus erythematosus as given by Libman

and Sacks, Gross, Baehr, Schifrin and Klemperer provided only a descriptive characterization of the disease.

3. The recognition of systemic alterations of the extracellular components of the connective tissue occurring in acute lupus erythematosus and allied diseases suggested an inquiry into the mechanisms by which alterations of these substances are provoked. Such investigations may lead to a pathogenetic definition of the maladies collectively termed "collagen disease".

4. Histochemical investigations of acute lupus erythematosus disclosed a disturbance of nucleic acid metabolism as one of the pathogenetic factors of the disease.

## SARCOIDOSIS IN RELATION TO TUBERCULOSIS

ELF MOSCHOCOWITZ

It is now accepted, largely through the studies of Schaumann (1) that lupus pernio described by Besnier; the uveo-parotid syndrome, by Heerfordt; the osseous lesions, by Jungling; the pulmonary lesions, by Kuznitsky and Bittorf; and the benign sarcoid by Boeck are different local manifestations of a generalized systemic disease, and the terms "sarcoidosis" or "Boeck's sarcoid" have been generally adopted. The unifying factor is the morphology characterized by tubercle formation, with epithelioid and giant cells. The lesion is supposed to differ from that of tuberculosis in that there is little or no necrosis, that there is little reactive peritubercular round celled infiltration, and that the disease usually runs a benign course.

Opinions on the cause of sarcoidosis have generated two camps: those who believe that the tubercle bacillus is *not* the cause of the disease and those who believe it is. Let us first review the submitted evidence *pro* and *con*.

1. The tubercle bacillus has not been found by many in any of the lesions of sarcoidosis by the conventional staining methods (2-17). On the other hand, but only in exceptional instances, tubercle bacilli have been found in cases that clinically and morphologically conformed to sarcoidosis. Schröpl (18) collected 26 case reports of sarcoidosis, in which tubercle bacilli were found. Obviously the absence of bacilli in a lesion that is morphologically tuberculous does not necessarily exclude a tuberculous origin, for it is well known that tubercle bacilli are not found as a rule in the older foci of tuberculosis. One may well conjecture whether the presence or absence of bacilli in the lesions of sarcoidosis is linked with a comparative study of early or late lesions. Most observers have contented themselves with a single examination, and there are but few reports where observations have been made at successive intervals. The results of these are highly illuminating. The earliest report and best observed is that of Kyrle (12). His patient presented a number of typical cutaneous sarcoids proven by biopsy. The tuberculin reaction was negative. After some weeks the lesions regressed spontaneously. In the course of the following two years, the patient had three febrile episodes, followed by an erythema precisely at the site of the previous lesions. After four or five days the erythema was followed by induration with the formation of nodules histologically typical of sarcoid; after a few months the nodules regressed completely leaving atrophic scars. Kyrle studied numerous successive biopsies. Up to the tenth day the morphology of the lesion represented a simple inflammation with a deposition almost exclusively of lymphocytes around the finer blood vessels. Within these areas a few epithelioid cells were seen. These areas stained well for tubercle bacilli. From the eleventh day the morphology assumed that of a sarcoid with many epithelioid cells. Stained tubercle bacilli could still be found but in smaller numbers. On the 36th day the fully developed lesion of sarcoid was complete with epithelioid and giant cells of the Langhans type and slight peritubercular infiltration with small round cells. The



tubercle bacilli could now no longer be seen. A biopsy taken on the 58th day showed vacuolated and degenerated epithelioid cells and the central portion of the tubercle showed slight caseation. The small round cells were more abundant at the periphery and the whole presented the morphology of early granulation tissue. A lesion biopsied on the 94th day showed dense connective tissue with capillary vascularization. A few epithelioid and an occasional giant cell of the Langhans type could still be found. At no time was the tuberculin reaction positive. The reports of Ruete (16) and Schröpl (17) confirmed this observation. In an early lesion of sarcoid they found typical tubercle bacilli; in biopsied material taken from the same lesion a few months later these organisms had disappeared. The significance of this observation will become apparent in a subsequent portion of this discussion. The cases of Kyrle, Ruete and Schröpl lent themselves particularly for such a study, since they were observed over a long period and presented fresh recurrences in association with older lesions.

2. Apparently the tubercle bacillus cannot be cultured from lesions removed by biopsy either in suitable media or by inoculation into animals. There are, however, some claims to the contrary. Schaumann (18) cultivated non-acid staining types of bacilli resembling diphtheroid and streptothrix types which gave positive complement fixation tests with Besredka's tuberculous antigen. He believed the bacilli to be of the bovine type. Ramel (19) Gans (20) and Jüngling (21) by successive inoculation into animals of tissue removed from a case of lupus pernio also obtained bacilli of the bovine type. Kyrle's observation is significant. He injected the blood of his patient, taken in the early phase of the lesions, into two guinea pigs. One died of typical miliary tuberculosis; the other remained unaffected. On the other hand, subcutaneous and intraperitoneal implantations of lesions removed even in the early stage when stained tubercle bacilli could be seen in sections, produced no tuberculosis. He regards these observations as proving not only a hematogenous mechanism for the production of the sarcoid lesions, but also that the bacilli in the skin had been killed by antibodies. This phase of the problem has been complicated by the reports of the finding of avirulent dissociated types of the tubercle bacillus in sarcoidosis. That dissociated forms of the tubercle bacillus do occur is an acknowledged fact. (For the literature see Mellon (22).) Employing the Hallberg method of staining the tubercle bacillus, Schaumann and Hallberg (23) demonstrated a mycotic form in a number of cases of sarcoidosis. They did not succeed in cultivating the organism or transmitting it to animals and they believe that the transformation was due to "anergy". This observation is supported by the claims of Mellon and Beinhauer (24). In an early lesion of sarcoidosis they isolated a partially nonacid actinomyces-like thread or a bacillary form of the tubercle bacillus and after many transplantations this developed into a strict acid fast form culturally indistinguishable from avian and human tubercle bacilli. They assume that in the beginning the highly susceptible skin is infected with real tubercle bacilli, but their virulence and biochemical properties are anomalous and that there is an early dissociation of this organism into either a frankly nonacid fast or partially acid fast form. They also showed experimentally that the acid fast culture with

which the patient was originally infected was capable of producing non-caseating lesions of the same general type as those found in the patient. They report that these organisms were capable of dissociating not only *in vitro* but also *in vivo* into one of the several types of nonacid fast organisms which were recovered from the patient. In a subsequent report (25) of a second patient they recovered the "diphtheroid" type of dissociation. Crawford (26) in another case found both the "actinomyceotic" and the "coccal" types of the tubercle bacillus. Mellon and Beinhauer maintain that these findings explain the failure of positive reactions with the conventional tuberculin. They manufactured a tuberculin from their dissociated types which produced a reaction in some of the anomalous cases. Previously, Miller (27) had succeeded in converting an acid fast tubercle bacillus into a nonacid fast type, and after transferring it to suitable media the organism reverted to the acid fast type, proving that the nonacid forms are specific.

The question arises whether these dissociations in sarcoidosis are the result of an inherent property of the bacilli or whether they are the result of an immunity in which the anergy may be an expression. There have been a number of attempts to investigate the precise nature of the anergy of sarcoidosis. Jadasohn (28) believed it was partly the result of anticutins which he believed to have demonstrated in rats, who are peculiarly non-susceptible to tuberculosis and who reveal the morphological and clinical evidences of sarcoidosis after inoculation with the tubercle bacillus.<sup>1</sup>

Pinner and his associates (29) found no specificity whatever in these anticutins and concluded that the presence or absence of anticutins was not significant in the diagnosis or pathogenesis of sarcoidosis. Lemming's (31, 32) investigation, if confirmed, is highly significant. He tried to verify in sarcoidosis whether the patient is absolutely anergic and therefore had been earlier infected with tuberculosis. He vaccinated a number of such patients with B.C.G. vaccine and although the regional lymph nodes showed unmistakable sarcoidosis, the patients' Mantoux reactions, even with as large a dose as 10 mgms., remained completely negative. Under ordinary circumstances, in individuals with a negative tuberculin reaction and who had not been previously infected with tuberculosis, the tuberculin reaction becomes positive after B.C.G. vaccination. Lemming, therefore, concludes that his experiments give strong support to the tuberculous origin of sarcoidosis, and that such individuals carry a special form of refractoriness manifested in the form of anergy. Significant in this connection is the observation of Reisner (33) that the average incidence of a positive tuberculin test in sarcoidosis is less than in the average cross section of the population. That refractoriness and not the physico-chemical properties of an anomalous type tubercle bacillus causes the relative lack of virulence of the tubercle bacillus in

<sup>1</sup> Kallos (30) believed that the rats unsusceptibility was the result of a Bartonella which invariably infects all laboratory rats, and which stimulate the reticuloendothelial system to lessen the virulence of the Koch bacillus. By spraying the rats with an arsenic and antimony preparation, blocking the reticuloendothelial system with India Ink and removing the spleen, he was enabled to produce a lethal caseating tuberculosis by inoculation with the tubercle bacillus.

sarcoidosis is indicated by the observations of Kyrle (12) and Warvinge (34) who injected virulent tubercle bacilli intracutaneously into the thigh of a patient with sarcoidosis and produced an infiltration morphologically identical to sarcoidosis. Lemming (32) showed that intracutaneous inoculation of B.C.G. instead of producing tubercles with necrosis, an invariable circumstance, caused the lesions of sarcoidosis.

3. Tuberculin reactions in sarcoidosis are usually negative (1, 5, 6, 8, 35-37). However, the incidence of positive tuberculin reactions is appreciable. Reisner (33) found a positive result in 40 per cent of his 35 cases; most of the reactions were weak. Lomholt (38) found a positive reaction in 18 per cent; a strong reaction was noted only in 2 per cent. Bernstein and Oppenheimer (11) found 4 positive reactions in their 6 cases, strong only in one instance. Longcope and Pierson (4) in seven cases noted a positive reaction in one. The report of a negative tuberculin reaction is usually viewed by most observers as an evidence of anergy, but as Rubin and Pinner (39) correctly argue, this conclusion is only justified when the tuberculin reaction is performed with sufficiently large doses of tuberculin. Reisner (33) and Hagn-Meinecke (40) noted a change in the tuberculin reaction from a negative to a positive one or an increase in the degree of sensitivity in several of their cases that developed frank tuberculosis under observation. In some the altered reactivity to tuberculin was found to have preceded the appearance of the clinical manifestations of active tuberculosis for a period of several months to years. This suggests, in Reisner's opinion, that "an increased sensitivity to tuberculin developing in a case of sarcoidosis may be more than a fortuitous circumstance and might signify a potential transformation into manifest tuberculosis". This observation had also been made by Schaumann (18), Munk (41) and Longcope (35). Rubin and Pinner (39) noted in one patient with a primary tuberculous infection a positive tuberculin reaction. Nine years later the patient developed the classical clinical evidences of a generalized sarcoidosis with uveo-parotid fever. A biopsy of a gland showed sarcoidosis. A Mantoux test at this time was negative. Three years later the intracutaneous tuberculin test (O.T. 1-10) was positive and at autopsy a caseous pulmonary tuberculosis was found.

Inasmuch as a positive tuberculin reaction represents a state of allergy its importance as a diagnostic differential has probably been over emphasized.

4. Although the morphological resemblance of the tubercle in sarcoidosis and in tuberculosis is close, certain points of difference have led many to deny the identity of the two diseases. These differences are: first, that the lymphocytic reaction in sarcoidosis is sparse; second, the giant cells are not as numerous and are not always of the Langhans type, and in many instances contain amorphous foreign bodies, having the appearance of calcific material (Schaumann (18));<sup>2</sup> and third, that caseation is absent or rare in sarcoidosis. The first and third represent only quantitative reactions and need not be seriously viewed as differentials. Kyrle's observation, previously referred to, indicates strongly that the

<sup>2</sup> These foreign bodies are not peculiar to sarcoidosis. They resemble precisely the concretions described by Metchnikoff (42) in rats infected with tubercle bacilli.



degree of these reactions depends on the stage of the disease. Indeed, our knowledge of sarcoidosis is largely inadequate because it has been studied from the static rather than the biological viewpoint. This applies not only to the morphology, but to the bacteriology and immunology of the disease. The presence or absence of caseation is entirely an arbitrary differential. Sarcoidosis in the last analysis is largely a clinical entity so that even those who regard sarcoidosis as nontuberculous, report occasional caseation (3, 6, 8, 36). Pinner (37) views sarcoidosis as the "non-caseating" form of tuberculosis and confirms Schaumann's impression that the caseating form of tuberculosis represents a direct transformation of the sarcoid lesions and not a separate process. Moreover there is evidence that the morphology of the tubercle depends to a considerable degree at least, upon the virulence of the strain. Medlar and Sasano (36) injected low virulent and high virulent strains of the human bacillus. The low virulent strain produced a tubercle like that of sarcoidosis with no caseation. In the older lesions the bacilli disappeared. With the high virulent strains, the tubercle was characterized by an acute inflammatory response with a predominance of polymorphonuclear cells and necrosis. These reactions were identical in allergic as well as in non-allergic animals. Smithburn (43) duplicated these results with bacilli of the bovine type. He views the acute reaction produced by the most virulent organism as due to properties associated with bacterial organism rather than to allergy.

5. Finally, a distinction between the two diseases has been made on the grounds that the two diseases are clinically dissimilar. Sarcoidosis differs from tuberculosis in that the clinical manifestations are usually very mild, the course is benign, and recovery is the rule, even sometimes with complete clinical disappearance of the lesions. Relapses however, do occur. It has been suggested that the occasional reports of the healing of "miliary tuberculosis" represent in reality cases of sarcoidosis. This clinical differentiation loses much of its validity when one reviews the many reports of associated lesions of sarcoidosis and tuberculosis in the same patient (14, 18, 35, 44-49); in most instances the tuberculosis follows upon what appeared to be a typical sarcoidosis. Furthermore it is particularly significant that in fatal cases of sarcoidosis the cause of death is, in the largest proportion, tuberculosis (3, 14, 18, 33, 37, 44, 45). For instance in the largest series reported, that of Reisner (33) five of the seven fatalities in which the cause of death could be established, were due to either pulmonary or miliary tuberculosis.

#### COMMENT

All the evidence favors the tubercle bacillus as the cause of sarcoidosis and indeed, the majority of the students of this disease maintain this view. It must be admitted, however, that these two clinical entities do not always dovetail and that an explanation must be forthcoming for the difference in the incidence of certain manifestations between the two disorders. This is particularly true of the difficulty one meets in sarcoidosis in detecting the organism in the lesion and in cultivating the tubercle bacillus, the infrequency of caseation, the comparatively mild clinical expression and the benign course.

These differences have led some to believe that sarcoidosis is due to an invasion



by the tubercle bacillus of the bovine type (18). Others believe that sarcoidosis is a form of leprosy, but only on presumptive evidence. Still others assume an unknown filterable virus. The Frei test has been uniformly negative. Williams and Nickerson (50) made an emulsion from a skin nodule and by intracutaneous injection obtained a reaction in four patients with sarcoidosis. The reaction was negative in controls. Harrell (8) could not duplicate these results. Kveim (51) prepared material from a sarcoid lesion and applied it intracutaneously. He obtained a positive test in 12 of 13 cases of proven sarcoidosis. The reactions appeared in one to four weeks and on biopsy, the lesions were like those of sarcoidosis. Controls, including cases of lupus vulgaris and syphilis, showed no reaction. Kveim concluded that the test was specific and of an allergic nature and that the disease was due to an unknown agent. Lomholt (38) did not find the reaction specific and found that the reaction was often delayed, sometimes up to 18 months. Putkonen (52, 53) agrees that the test is of diagnostic value, but that the reaction is not specific. Of 42 cases of sarcoidosis, 33 were positive. He also obtained an antigen from a leukemic gland which also gave a specific reaction. Danbolt (54) on the other hand, found the Kveim reaction specific and argues therefore that the disease is not tuberculous. Warvinge (34, 55) reproduced the Kveim reaction with both living and dead tubercle bacilli, and is therefore inclined to believe that the Kveim reaction represents an implantation with anomalous tubercle bacilli. In view of the investigations of Sabin and her coworkers (57) (which will be subsequently reviewed) that certain lipid phosphatid fractions of the tubercle bacillus when injected cause lesions morphologically identical with those of sarcoidosis, it is not unreasonable to infer that the Kveim reaction may be the result of the same mechanism. Observations on the validity and mechanism of the Kveim reaction necessitate more work and confirmation than is at present available.

Curiously, an almost forgotten observation made nearly fifty years ago would seem highly significant in the interpretation of many of the obscure relations between tuberculosis and sarcoidosis. Prudden and Hodenpyl (56) in 1891 injected rabbits intravenously with killed tubercle bacilli. Tubercles in the lung appeared on the fifth day and persisted to the end of the second month. These tubercles were composed of epithelioid cells and a centrally situated giant cell and the whole was interspersed and surrounded by round cells. In the later stages these nodules appeared denser and the dead tubercle bacilli could be stained in small numbers. In the third to fifth week the lungs assumed the appearance of a miliary tuberculosis. As early as the third week tubercles appeared in the liver in which bacilli could be found. In the fourth to sixth week the liver contained many miliary tubercles with epithelioid and giant cells. The bacilli disappeared in all tubercles at the end of the sixth week. At no time did caseation occur even at the end of the seventh week. Prudden and Hodenpyl's findings have been confirmed (57-60). Vissman (61) obtained identical results by dead bacilli heated in Ehrlich's carbol-fuchsin. In other words, the fully developed lesions after the injection of dead tubercle bacilli were identical with those conventionally deemed typical of sarcoidosis, in respect to morphology, distribution,

the absence of caseation, the disappearance of bacilli and the tendency to involution. It appears that viability is not essential to the production of a tubercle and that dead tubercle bacilli contain a substance in the nature of a foreign body that stimulates the formation of tubercles without necrosis, and the summation of the process is accompanied by a disappearance of the bacilli with healing.

Attempts to isolate this substance have been made by a number of investigators. Morse and Stott (62) in 1916 extracted a substance from masses of tubercle bacilli that possessed the physical properties of a wax which they injected into rats. At the end of four weeks typical tubercles consisting of epithelioid and giant cells but without caseation developed. The wax had not yet disappeared, but was still present in giant cells and in tissue spaces surrounded by avascular granulation tissue. The animals showed no cachectic phenomena or other abnormalities. Numerous other successful attempts have since been made by various methods of extraction from tubercle bacilli; these have been summarized by Sabin (63). The most complete studies in this direction were made by Sabin, Doan and Forkner (64) who found that various lipoid fractions of the tubercle bacillus, notably a substance which they call phosphatide A3, and a constituent of this phosphatide called pthioic acid, produced typical tubercles when injected into animals. These tubercles resembled precisely those of sarcoidosis even though occasionally small areas of caseation were noted. The protein fractions and the polysaccharides did not produce tubercles. These tubercles are innocuous and are completely absorbed. These findings have since been confirmed by Roulet (59). In a later communication Sabin, Smithburn and Thomas (65) produced tubercles by the injection of unsaponifiable wax derived from human tubercle bacilli. In these tubercles some of the giant cells contained wax in smaller and larger particles resembling somewhat the peculiar foreign bodies seen by Schaumann and others in cases of sarcoidosis. Smithburn and Sabin (66) also found that injections of the tuberculo-phosphatid does not induce hypersensitivity to tuberculin.

These observations of Prudden and Hordenpyl, Sabin, and others do much to reconcile the many differences herein cited between those who uphold the tuberculous origin of sarcoidosis and those who do not. The development of typical morphological lesions of sarcoidosis by dead tubercle bacilli or their products explains the comparative absence of bacilli in sarcoidosis, the remarkable freedom from tuberculin reactions and the comparatively mild clinical expression. Whether the lesions of sarcoidosis arise from bacilli that were primarily dead or whether the bacilli were of a dissociated type and comparatively inert or whether originally virulent bacilli were destroyed by the immunity of which the anergy may be an expression cannot be decided with certainty, but the evidence is in favor of the last supposition. When active tuberculosis supersedes sarcoidosis, it is presumed that either the patient has lost his immunity or there has been a fresh invasion by virulent tubercle bacilli or that there has been a reversion *in vivo*, as Mellon and Beinhauer claim, from a dissociated type of tubercle bacillus to the virulent form. When sarcoidosis follows an active tuberculosis the reverse relations probably supervene.

## SUMMARY

The arguments for and against the tuberculous origin of sarcoidosis have been presented. Evidence has been submitted that points clearly to the fact that sarcoidosis is the result of the invasion of the body by dead or avirulent tubercle bacilli, and that in all probability, these have been rendered so by the extraordinary anergy that prevails in this disease.

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## PEPTIC ULCER—PRESENT-DAY MEDICAL THERAPIES

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*Introduction:* Peptic ulcer is a common disease probably afflicting 5 to 10 per cent of the adult population. Its etiology is unknown. The chief theory held today is that it is a psychosomatic disease in which psychic influences disturb the gastric functions so that excessive secretory, motor, and vascular activity leads to peptic ulcer. Both external aggressive or irritant factors and tissue susceptibility are involved, in that frequently increased secretory and motor activity acts on a mucosa made susceptible by circulatory changes (either hyperemia or anemia), and probably deficient protective substances (decreased mucus).

The localization of peptic ulcer may perhaps be best explained by mechanical factors acting on the lesser curvature, in the prepyloric region, and in the duodenal bulb.

Erosive gastroduodenitis is a preceding stage, or an accompaniment, or a substitution for the ulcer itself and probably results from the same factors as those concerned in the solitary ulcer.

While peptic ulcer is in most instances the result of a neurosis, it is not necessary to assume that all peptic ulcers are psychic in origin. There are certain groups which may have another etiology. For example, peptic ulcer in adolescence and at the menopause (ductless glandular?), in old age (arteriosclerotic?), and in certain geographic areas (Italian seacoast, Abyssinia, and India) where dietary irritants may be causal in the high local incidence of the disease.

Not only the ultimate causes as just discussed must be considered, but also the immediate mechanism of ulceration. In this phase of the problem there is less disagreement. Most authorities consider the chief pathologic-physiologic gastric changes in peptic ulcer to be the following:

- (a) hypersecretion (acid and pepsin) especially in the interdigestive phase;
- (b) hypermotility, including increased tone and peristalsis;
- (c) vascular changes (either hyperemia or anemia);
- (d) diminished tissue protection (lessened alkaline substances, including the various types of mucus and possibly increased lysozyme).

It should be noted here that most all of these changes indicate hyperfunction. The concept of prolonged hyperfunction on a psychogenic basis is a favorite etiologic hypothesis today.

It has been necessary to introduce the therapy of peptic ulcer with this preliminary discussion, since some basic concepts of the etiology of the disease seem necessary for rational therapy.

It is the purpose of this paper to consider some recent ulcer therapies in the light of these etiologic moments.

*Sippy Therapy:* This conventional, current therapy of peptic ulcer is based on the principle of continuous neutralization of the gastric acidity. It consists in frequent, hourly, bland feedings, chiefly of milk and cream, to adsorb and dilute the acid, interspersed by hourly administration of large amounts of absorbable alkali for neutralization.

This form of therapy fails in its chief objective, namely, the attainment of a continuous neutralization (1). It has been demonstrated that aspiration of the gastric contents between the feedings, especially immediately preceding them, reveals a large amount of free acid during the day. It also has other serious objections:

- 1) It is nutritionally inadequate during the first three weeks;
- 2) The frequent feedings stimulate the cephalic or nervous phase of gastric secretion;
- 3) The large amount of absorbable alkali often leads to undesirable bodily alkalosis resulting in renal damage, nervous symptoms, and in rare cases, even tetany;
- 4) It does not control the night secretion (2) even when gastric aspiration, before retiring, is practiced; and,
- 5) It fails in the refractory group which comprises approximately 25 per cent of the uncomplicated peptic ulcers.

Why then, it may be asked, does it seem to be a successful therapy in 75 per cent of the uncomplicated ulcers? The answer probably lies in the fact that that percentage either tends to go into remissions spontaneously as part of the natural course of the disease, or, the psychologic influence of the therapist, rather than the therapy itself, is responsible for the temporary good result.

It would perhaps be better to drop the Sippy therapy in the group of mild, uncomplicated ulcer patients and to substitute the following therapeutic regimen:

- a) A liberal ulcer diet, i.e. three main feedings with a small feeding between these meals and before retiring;
- b) a vagal depressant drug before the meals; and,
- c) a non-absorbable alkali after meals and before retiring, such as aluminum hydroxide or phosphate gel.

*Co Tui Therapy:* Protein hyperalimentation in the form of 350 to 450 grams of aminoacid mixture plus an equal amount of Dextri-Maltose (No. 2) in 1500 cc. of water, divided and fed at two hourly intervals during the day, was introduced by Dr. Frank Co Tui in 1945 (3). It was based on the chance observation that intravenous aminoacids caused remarkable improvement in some ulcer patients who were being prepared for surgical therapy because of hemorrhage or pyloric obstruction. Co Tui then based the oral therapy of peptic ulcer with such a mixture on the following:

- a) The usual protein intake is too low in the conventional ulcer therapies;
- b) there is an improvement in experimental wound healing with protein hyperalimentation; and,
- c) the buffering and neutralizing effect of the mixture on the gastric acidity is of value.

Several observers have confirmed the idea of the buffering and neutralizing effect of the mixture on gastric acidity. Doctors Norman Samuels, Franklin Hollander and the author have found that when the stomach is aspirated midway between the two hourly feedings that pH's of 3.5 to 4.5 are the rule. However, we found that this acidity control did not extend into the night. After the last feeding, usually at 10 P.M., the stomach, as in the Sippy therapy, reveals large

amounts of highly acid peptic secretion throughout the night. However, if the continuous intragastric drip of the Co Tui mixture, the milk-soda mixture, or the Hollander aliment is added during the night to the Co Tui therapy during the day, the night acidity is controlled and pH's at or above 3.5 are obtained.

The favorable features of the Co Tui therapy are the following:

- 1) The bland liquid diet;
- 2) the high caloric value;
- 3) the fact that the unpalatable mixture lessens the psychic secretion; and,
- 4) the buffering value.

In most cases it is only possible to continue this form of therapy for a short period. The symptoms often tend to recur with the discontinuance of the treatment.

It would seem worth-while to try this form of therapy plus the continuous intragastric drip in refractory but uncomplicated ulcer patients. It would appear, therefore, to have some value in a properly selected group of patients.

*Enterogastrone:* This inhibitory hormone or "chalone" is evoked by the presence of neutral fat and hypertonic sugar solutions (over 10 per cent) in the duodenum and upper jejunum. Its physiologic function is to inhibit the hormonal phase of gastric secretion, presumably by antagonizing histamine and to lessen the gastric motor activities. Using extracted and purified preparations of enterogastrone, Ivy and his co-workers were able to demonstrate in the experimental ulcer of Mann-Williamson dogs, ulcer-preventing, ulcer-healing, and ulcer-immunizing properties in this substance. Ivy also treated a series of human ulcer patients with enterogastrone on the basis of this experimental work and claimed some good results (4). In his studies of the recurrence rate in the individual's ulcer history, he was convinced that the ulcer-immunizing benefit of enterogastrone was obtained, although not to a great degree. However, these good results have not, as yet, been confirmed (5). Furthermore, it has been demonstrated that, in the dosage suggested by Ivy, neither the day nor the night secretion is reduced in human ulcer patients (6). Whether there exists an actual decrease in this "chalone" in ulcer patients is, of course, at the present, entirely conjectural. Perhaps improved preparations, larger dosages, and further studies will reveal better results in the future with this form of therapy.

*Psychotherapy:* The idea that peptic ulcer is a psychosomatic disease in which emotional disturbances so effect the functioning of the stomach that ulcer results, is steadily gaining in popularity. Final proof of this hypothesis is not at hand, since neither the production of peptic ulcer through psychic means nor the complete cure of peptic ulcer by psychotherapy has been demonstrated. However there are many arguments which speak in favor of this view. Among them may be listed the following:

- 1) The frequent onset of peptic ulcer and ulcer recurrences following emotional traumas;
- 2) the increase of ulcer incidence in whole populations under stress, such as during warfare;
- 3) the onset of ulcer at adolescence and menopause which are notoriously periods of considerable emotional strain;

4) the well-known, profound effect of emotional disturbance on gastric physiology and the evidence that these disturbances are mediated through nervous pathways (chiefly the vagus nerves); and,

5) not infrequently, good temporary therapeutic results are induced by psychotherapy.

There are, of course, numerous knotty problems connected with the psychologic approach. For example, the pathologic physiology involved in the pathogenesis of peptic ulcer is not entirely clear. Wolf and Wolff have concluded from their study of Tom, a patient with long-standing gastric fistula and a stenosed esophagus, that anger increases the acidity, the motor activity, and the vascularity, and that these states, if prolonged and severe, may lead to peptic ulcer (7). Fear, on the contrary, lessens the gastric functioning. They doubt if this type of emotional disturbance, fear, plays a role in the ulcer disease which is notoriously one of increased functional activity in the stomach.

During the past  $2\frac{1}{2}$  years, we have studied a young, adult female, who has had a large gastric fistula with a stenosed esophagus for five years. Our methodology in this study consisted in psychoanalytic interviews 3 to 5 times weekly, and parallel physiologic studies three times weekly. In this patient we found that both anger and fear induced either increased or decreased gastric functioning. We also noted in her a remarkable phenomenon in that certain unconscious emotional states were associated with a dissociation of her various gastric functions (8). Normally, the five functions of the stomach, namely, volume, acidity, peptic activity, motility, and vascularity, following the usual external or internal stimuli, fluctuate in an associated or synchronous fashion, that is, they tend to rise or fall together.

This brings out then another possibility in the problem of peptic ulcer, which is that not only hyperfunction may lead to the disease, but perhaps a dissociation of the gastric functions may be involved. For example, if a dissociation between the motor and secretory functions (increased secretory and decreased motor activity?) or an increased secretion of acid and a decreased secretion of mucus were demonstrated, then this phenomenon of dissociation may assume considerable importance, since such states are obviously harmful. Inasmuch as the psychological unconscious seemed to be the potent determinant of these dissociated changes in our fistula case, it would seem necessary to study the role of the unconscious in peptic ulcer. It seems probable that conscious emotional states, while also of importance in abnormal organ functioning are less significant than the unconscious states. This leads to the suggestive conclusion that psychoanalysis may prove to be a fruitful field both for the investigation of the etiology and therapy of peptic ulcer since its chief purpose and method is the investigation of the unconscious. Despite these statements, the value of the superficial approach to the patient's conscious daily problems by the general practitioner, internist, or gastroenterologist should neither be overlooked nor denied. Careful studies of series of ulcer cases approached by the psychoanalytic method are eagerly awaited as well as the results of other forms of psychotherapy.

*Continuous Intragastric Drip Therapy:* In 1931, the intragastric drip therapy was introduced for peptic ulcer. This therapeutic procedure is based on two ideas:



1. Whatever the ultimate cause of peptic ulcer may be, free hydrochloric acid plus pepsin is a prime factor in the development and persistence of the lesion.
2. Methods which are most effective in the neutralization of the free acidity throughout the twenty-four hours of the day are most likely to be successful in the medical therapy of peptic ulcer. Previous methods of controlling the interdigestive secretion had been found inefficient, particularly throughout the longest interdigestive period, viz., the night. Therefore, the drip therapy was devised as a logical method of attaining this goal. The efficiency of the drip method in neutralizing gastric acidity is illustrated by studies which indicate that both the milk-sodium bicarbonate mixture and diluted alumina gel preparations are effective in raising the gastric pH on the average from 1.5 to 4.0 in the interdigestive periods. Since free acid does not exist above a pH of 3.5 and since 90 per cent of peptic activity is eliminated at this pH, the digestive action of the hydrochloric acid-pepsin mixture is practically eliminated by this procedure, particularly during the night, when other forms of medication are usually discontinued (2).

The drip acts continuously and regularly, and its effectiveness may be due in part to the rationale of giving small doses of an antacid continuously rather than large doses intermittently. As pointed out, Sippy feedings serve as a stimulus to increased acid secretion. Certainly it is not logical to protect the ulcer crater for half of the day in order to allow granulation tissue to form and then to expose it to the strong corrosive action of gastric juice for the remainder of the twenty-four hours. Originally the drip was administered continuously throughout the twenty-four hours of the day for two or three weeks. In recent years the treatment has been modified as follows: The patient receives three liberal bland meals daily with Atropine or Banthine and the usual sedatives and post-prandial alkalies. One hour after each meal the drip is started, and it is continued until one hour before the next meal, and throughout the night. Patients with milder but refractory symptoms may take the conventional ulcer therapies during the day and the intragastric drip at night only for several weeks.

Since 1934, the use of non-absorbable alkalis for antacid therapy has become increasingly popular. Of these various preparations, gels of aluminum hydroxide and phosphate have the further advantages of being astringent and anti-peptic. Also, when diluted, they lend themselves readily to use in a drip apparatus. Hence these two colloidal preparations can be substituted for the milk-sodium bicarbonate drip in conditions in which the latter is contraindicated.

Since the drip therapy was instituted 19 years ago, many hundreds of patients have been treated by means of it. Sixty cases have been studied carefully and were presented to illustrate the fact that certain patients with severe ulcers who were refractory to the conventional ulcer treatment (i.e. Sippy) may be relieved by the administration of the drip. In most of these cases drip therapy was not begun until all other measures had failed.

Certain conclusions concerning this form of therapy may be presented:

- (1) It is a successful method for the adequate control and neutralization of the gastric acidity throughout the day and especially during the night.

(2) The method, easily learned, gives the patient a means of self-therapy at home for long periods during the night without interfering with his daily work.

(3) Most cases require it only at night. However, moderate and fairly severe cases require the drip between the meals and during the night.

(4) Three liberal, bland 'ulcer meals', supplemented with aminoacids, preceded by atropine and phenobarbital or Banthine, followed by alumina gel, when combined with interdigestive and nocturnal drip, permit adequate, maximal tissue nutrition and provide, at the same time, optimal neutralization.

(5) Very long remissions have been seen, which are particularly significant in view of the refractory type of patient placed on this therapy.

(6) It is an excellent method of controlling the distressing night symptoms without disturbing the patient's sleep.

(7) While no claim is made for this therapy as a complete and permanent cure of the ulcer disease, it seems to be in the light of our present ignorance of the true, ultimate cause of peptic ulcer a logical and practical attack on the central agent or mechanism of ulcer production, the acid (or 'acid pepsin') factor.

(8) Other ulcer therapies apparently do not adequately control the harmful interdigestive, nocturnal acid-pepsin secretion.

*Banthine:* This drug is a quarternary amine which belongs to the group of pharmacologic agents which effect an autonomic blockade. It also has, in moderate dosage, a strong atropine-like action at the post-ganglionic nerve endings of the parasympathetic system. It has three important properties:

(1) It is effective orally.

(2) In clinical doses its action is apparently stronger than atropine.

(3) No acute or chronic toxic effects from the usual dosage employed have been noted.

Its effects on the motor and secretory functions of the stomach in humans and in animals have been studied (9). It apparently diminishes contractions and motility markedly. The volume of secretion and the free acid are also decreased.

The value of the use of this type of drug in patients with peptic ulcer is apparent. A considerable array of evidence may be marshalled in favor of the view that irrespective of what the ultimate cause of peptic ulcer may be, heightened vagus nerve activity seems to be of central importance in the problem of ulcer etiology and therapy. The following may be cited:

(a) The acid peptic secretion and motility and vascularity is stimulated by vagal action.

(b) The interdigestive secretion, usually markedly increased in duodenal ulcer, is probably vagal in origin.

(c) Vagotomy has produced some strikingly good results.

(d) The secretory response to insulin hypoglycemia, which is due to the dorsal vagal nucleus, is excessive in ulcer patients as compared with normals. It is, therefore, obvious that a good depressant of the parasympathetics (i.e., the vagus nerves) should be a valuable therapeutic agent in peptic ulcer. Banthine may prove to be such a desirable agent.

Since Banthine was only recently introduced, there are but a few clinical studies to date with a short follow-up period. Dr. K. Grimson recently reported his results with this drug before the New York State Medical Society (10). One hundred patients with ulcer were treated with Banthine alone, without any special diet or other therapeutic measures. He advocated strongly a dosage of 100 milligrams before each meal, before retiring, and once during the night. The patients had considerable atropine-like side-effects with this dosage such as oral dryness, blurring of vision, and some difficulty in urination. He claimed that after a few days these symptoms disappear. In Grimson's series the clinical results seem quite good, since only five of these rather severe cases came to surgery during the year of observation. The others lost their symptoms quickly. However, the disappearance of duodenal ulcer craters often took from 100 to 270 days.

Our studies with Banthine are, of course, preliminary. They may be summarized briefly.

*Clinical Studies:* Forty ambulatory patients with duodenal ulcer who were refractory to the conventional ulcer therapy consisting of belladonna, a liberal diet, and non-absorbable alkalis, were treated with the same routine, with the single exception of the substitution of Banthine for the belladonna. Most of these cases were treated with 50 milligram doses. Six patients refused the drug, even in this dosage, because of the unpleasant side-effects. The others had minimal side-effects and exhibited an excellent clinical response. Two cases are selected for presentation:

*Case 1:* A young, adult, male, who developed 10 days after a subtotal gastrectomy without vagotomy for a severe duodenal ulcer, a recurrent jejunal ulcer. A large, penetrating, jejunal ulcer developed with severe day and night pains, which, despite one year of conventional ulcer therapy plus psychiatric advice, did not improve. On 100 milligrams of Banthine, 5 times daily, he lost his symptoms completely, and in two months the ulcer crater had diminished to the size of a minute projection. He remains symptom-free for three months on Banthine therapy.

*Case 2:* A middle-aged male, with gall stones and a duodenal ulcer, was treated for three months with the full dosage of Banthine. He lost his ulcer symptoms; and the radiographs revealed some improvement in the ulcer crater. He then developed, while on Banthine therapy, some upper abdominal pains and surgical therapy was advised. A chronically diseased gall bladder, containing stones, was removed. A rather large open ulcer crater on the superior border of the duodenal bulb was also present. For this, a bilateral infradiaphragmatic vagotomy and gastroenterostomy were performed.

In general, the symptomatic response of this drug has been strikingly good. However, a large series of cases, prolonged observation, radiographic and surgical studies, and further experimental work will all be necessary before reaching the final conclusions concerning the real value of this drug. Of greatest importance will be the question as to whether Banthine merely induces a symptomatic relief without healing as in Case 2, or whether the loss of symptoms will be accompanied in some or all of the cases by definite evidence of healing of the lesion as in Case 1.

*Physiologic Studies:* In some cases, the continuous or fasting secretion was abolished by 100 milligrams of Banthine, and in others it was unaffected. This,

also, held true for the nocturnal secretion. Banthine did not prevent the secretory rise following the gruel test meal. Also, the secretory response to 15 units of intravenous Insulin was not prevented. The response to a small dose (5 units) was abolished in two of three cases. Also, the response to a small dose of histamine phosphate (0.25 mgm) was abolished, but not to a larger dose (0.5 mgm). Apparently, the effect on gastric secretion is inconstant. The symptomatic relief from Banthine may be due chiefly to its effect on the motor activities of the stomach. There is also a possibility that it blocks the afferent impulses through the sympathetics.

#### SUMMARY AND CONCLUSIONS

- (1) The Sippy therapy for peptic ulcer, because of the many objections cited in the text, should be discontinued.
- (2) For mild uncomplicated cases, 5 meals daily with vagal depressants and antacids should be substituted.
- (3) For moderate and severe cases a combination of this type of therapy or of the Co Tui hyperalimentation therapy, plus the continuous intragastric drip during the night, is advocated.
- (4) In severe, refractory, but uncomplicated ulcers, a trial of the intragastric drip therapy continuously, that is, 24 hours daily, for several days is advocated before resorting to surgical therapy.
- (5) Results of enterogastrone therapy to date have not been impressive. Further studies seem necessary.
- (6) Psychotherapy, since it is aimed at the ultimate cause of the disease, should be pursued vigorously. Intensive and prolonged psychophysiologic and psychotherapeutic studies are urgently needed in patients with peptic ulcer.
- (7) The new parasympathetic depressant drug, Banthine, gives sufficient promise to warrant an extensive study of its use in ulcer patients.

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# MULTIPLE EROSIONS AND ACUTE PERFORATIONS OF THE ESOPHAGUS, STOMACH AND DUODENUM IN RELATION TO DISORDERS OF THE NERVOUS SYSTEM\*

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Clinician and pathologist, alike, have been aware for quite some time of the not infrequent occurrence of "black vomit," so-called because of the characteristic appearance of the ejected material. It has been described in more recent times by Beneke (1) as being composed of slimy gastric contents, mixed with varying amounts of brownish-black, coffee-grounds material, often containing rounded masses of coagulated blood, which assume, in the more severe cases, the form of black, tarry masses. While in the earlier days this type of vomitus was a common feature in the terminal stage of yellow fever and similar morbid states, the physician and surgeon of today encounter it in a variety of grave systemic diseases and particularly following surgical intervention. The vomiting occurs precipitantly and is usually associated with a general collapse, the latter either preceding or following it. Most commonly, the hematemesis is found to be an ominous sign, although instances in which recovery has followed are not rare.

In some fatal instances, the gastrointestinal tract came under the surveillance of the pathologist and, not infrequently, an explanation for the bleeding was found in the discovery of multiple hemorrhagic defects in the mucous lining of the upper gastrointestinal tract. Cruveilhier (2) was first to describe and illustrate in color such lesions under the term of *hemorrhagic erosions*. Subsequently, these erosions came under the scrutiny of the two pioneers in modern pathology: Virchow (3), and Rokitsansky (4). The former advanced the view that these lesions were the result of local vascular disease, while the latter suggested a disturbance in some part of the nervous system as the probable cause.

About the beginning of the 20th century, as the era of vigorous physiological investigation had set in, studies were initiated in an effort to re-evaluate all possible factors involved in the development of the lesions under discussion. A variety of opinions were expressed. Foremost among them was embolization of terminal vessels in the affected mucosa as the cause of the necrotic mucosal alterations. But this view met with serious opposition in the investigations, observations, and speculations of Beneke and his co-worker (1), and it seems, therefore, most appropriate to sum up their work at this point.

Beneke found many flaws in the general views held in his day as to the probable etiologic factors responsible for the multiple ulcerations of the upper gastrointestinal tract. But before presenting his own view he deemed it necessary to first define more clearly the morphologic nature of the lesions. He objected to the term "hemorrhagic erosions" as being incorrect, as some, and often many, of the multiple ulcerations are free of hemorrhage. He offered instead the more inclusive term "*stigmata ventriculi*" which has as its advantage a more flexible interpretation. He did not realize, however, that the proposed term was also

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too self-limiting as it would restrict the lesions to the stomach (ventriculus), while they are frequently found in the duodenum as well as in the lower part of the esophagus. He further specified the character of the lesion by describing it as being a wedge-shaped ulcer, limited to the mucosa, only seldom extending beyond it. It is small in dimensions, occurring usually in large numbers, widely disseminated, and is the apparent source of bleeding in many cases. Beneke dismissed the previously expressed theories of their causation, except those, in which the nervous system was regarded as the seat of the provocative disorder. He advanced the concept that a dysfunction of the neural mechanism causes transient ischemia of many parts of the mucosa. This, in turn, leads to devitalization of the affected areas. Coincidentally, as a result of the same abnormal neural functions, there is an increased secretion of acid, which, when acting upon the devitalized portion of the mucosa, ultimately leads to the ulcerations. Beneke, in formulating this neuronal hypothesis was, of course, not only cognizant of the view held by Rokitsansky, but also of the experimental work of Brown-Sequard (5), Schiff (6), and Ebstein (7), who were able to produce alterations of a similar nature by inducing lesions at several levels of the cerebrospinal axis, and in the peripheral nervous system. Moreover, Kobayashi (1), under Beneke's direction, repeated some of this earlier experimental work and added experimental data of his own. He was able to produce the so-called stigmata ventriculi by transient occlusion of the coeliac artery, by injecting adrenalin into the muscularis of the stomach, by sectioning the spinal cord, following this by the feeding of acid, by irritation and by section of the coeliac plexus and by ligation of one or both vagal nerves at the cardia.

Beneke (1) has also presented the results of a survey of his own 400 cases in which bleeding into the lumen of the stomach took place. Of these, 165 exhibited the stigmata; 11 showed stigmata with ecchymoses, while the majority of the remainder showed either simple ecchymoses or no anatomical grounds for the bleeding. Unfortunately, he was not too precise in describing his cases, particularly those in which there was a concomitant disorder of the central nervous system. Nevertheless, his observations permit two important conclusions: first—that in the non-operated cases the stigmata were most often associated with some form of disease of the nervous system, while simple ecchymoses were most commonly seen in cases of disturbed function of the heart, lungs or kidneys; second—that in those instances in which a nervous disorder was present, the disease was not usually a circumscribed one, but diffuse, or disseminated. His observations do not permit the identification of any special area in the central nervous system which can be held responsible for the stigmata.

In presenting clinical evidence favoring a disturbance in the neural mechanism as the cause for these phenomena, Beneke was not alone. Shortly after Rokitsansky made his contribution to this problem, Hoffman (8) reported perforation of the esophagus followed by peritonitis in a case of an interpeduncular tumor with softening of the pons and medulla oblongata. Arndt (9, 10) described hemorrhagic erosions of the stomach in association with a median cerebellar tumor. Two cases of inexplicable fatal bleeding following suboccipital craniectomy were reported from von Eiselberg's clinic (11). Mogilnitsky (12) recorded 3

cases of hemorrhagic erosions, finding in one a frontal lobe tumor, an ependymal tumor of the 4th ventricle in another, and in the third, "sclerosis" of the mid-brain with hydrocephalus and meningitis. Von Preuschen (13) reported a case of subtentorial hemorrhage in an infant who exhibited at death hemorrhagic erosions in the stomach. Von Reuss (14) made the observation that cerebral birth injuries may predispose to such erosions. Blackfan (15), in a personal communication to Cushing, reported 4 cases of esophageal perforations in children, 3 of whom had meningitis and 1 an obstructive hydrocephalus caused by an aqueductal lesion. Some observers, including Klemperer, Penner and Bernheim (16) considered such stigmata to be preterminal "shock" lesions and postulated a mechanism not unlike the one suggested by Beneke, implying some reflex discharge of the autonomic nervous system.

There still remains, however, a fairly large quota of cases with stigmata, devoid of a primary disease of the central or peripheral nervous system. This is true of several systemic diseases, with yellow fever as a striking example. The so-called Curling's ulcerations which occur in association with severe and extensive burns are strikingly similar to the stigmata. However, in many of these cases, careful studies of the central nervous system are lacking. In the case described by Globus and Bender (17), these lesions were found associated with a disseminated toxic degenerative encephalopathy. Similar lesions in the gastrointestinal tract were first described by Dieulafoy (18) in toxic pneumonia. Finally, consideration must be given to Selye's (19) description of the multiple gastrointestinal ulcerations with hemorrhage as one of the phenomena appearing during the alarm phase of the adaptation syndrome.

From the foregoing it would seem that the consensus, at present, is that the stigmata, affecting not only the mucous membrane of the stomach, but also that of the duodenum and esophagus, (and probably also acute perforations) are to be considered as an expression of a disordered function of some part of the nervous system. It was Cushing (15) who, by surveying the literature and adding his own observations, placed emphasis on the neuronal factor in the causation of the erosions. He summed up his views by saying: "Those favorably disposed towards the neurogenic conception of ulcer have, in the process of time, gradually shifted the burden of responsibility from the peripheral vagus to its center in the medulla, to the midbrain, and now to the interbrain, newly recognized as a highly important, long overlooked station for vegetative impulses easily affected by psychic disturbances." He went a step further in projecting his own view by selecting the hypothalamus as the center which, when affected by disease or injury, is responsible for the gastrointestinal erosions. This conclusion has aroused deep interest among the pupils and followers of Cushing and served as an inspiration for a large series of experimental and clinical studies with the hypothalamus as the central point of the investigations. With this, the concept of hypothalamic control over gastrointestinal activity became firmly rooted in neurologic literature and has become the basis for a lively discussion of the probable psychosomatic factors operative in the etiology of chronic peptic ulceration.

With the aforesaid in mind, and in order to determine the existence or absence



of accord of the available clinical and experimental data with the views held regarding the origin of these erosions, a resurvey of the literature was undertaken and was supplemented by observations of our own. The latter aim at the determination of certain facts concerning the natural history of the gastrointestinal erosions; their incidence in general autopsy material, their relationship to disturbances of the nervous system, the types of nervous system disease seen in association with erosions, and finally, the question as to whether an isolated lesion of the nervous system, central or peripheral, can be held responsible for the formation of stigmata, and whether (as Cushing hypothesized), this must necessarily involve the hypothalamus or its descending pathways.

### The Experimental Contributions to the Problems

The experimental production of focal destructive or irritative lesions in the nervous system with the aim of inducing erosions in the gastrointestinal tract was begun early in the second half of the 19th century. Roughly, this period may be divided into two parts: one preceding the Cushing era and terminating in 1931-1932; the other, following it.

As early as 1844, Schiff (6) had shown that lesions produced at various points of the cerebrospinal axis in dogs and rabbits, resulted in acute erosions and perforations of the gastrointestinal tract. This was accomplished by sectioning the thalamus and the ipsilateral peduncle by hemisection of the pons and caudal medulla oblongata and by hemisection of the upper cervical spinal cord. Ebstein (7), in 1874, obtained such erosions by the creation of minute lesions in the superior colliculi, by unilateral lesions in the thalamus, medulla oblongata, and the upper cervical spinal cord. He also succeeded in provoking such lesions after traumatizing the lumbar spinal cord, the labyrinths, and also by dividing and stimulating the sciatic nerve. Brown-Sequard (5), in 1876, found that by producing lesions at the junction of the middle cerebellar peduncle and pons, he was able to obtain hemorrhagic erosions in a large number of experiments. Von Preuschen (13), in 1894, and Pomorski (20) succeeded in inducing pulmonary and also gastric hemorrhages after making punctate lesions in the crura cerebelli, corpora quadrigemina, and the floor of the 4th ventricle. Results were most frequently obtained by the injection of chromic acid into the right anterior colliculus.

Burdenko and Mogilnitzki (21), in 1926, were the first to direct attention to the hypothalamus. They employed a subtemporal approach for the production of destructive lesions at the base of the brain, behind the infundibular stalk, and in this manner were able to produce gastric erosions. Keller (15) is quoted by Cushing to have made bilateral lesions in the region of the hypothalamus, in the belief that he was freeing it from its connections with the brain stem. The animals died on the 4th to 10th day after the operation and subsequent examination disclosed gastric lesions ranging from acute hyperemia to punched out ulcers. Keller, Hare and D'Amour (22), reported in 1933 the results of operations they performed on 50 cats and 40 dogs. Lesions were made in the upper part of the brain stem (the authors do not specify the number of lesions made at each level).

Acute gastrointestinal changes were observed to have developed in a relatively small number of the experimental animals. In the entire series of 90 animals, erosions were found in only 3 cats with lesions of the midbrain and in 8 dogs with transverse hypothalamic lesions at the level of the optic chiasm and with hemorrhage into the ventricles.

Somewhat later, Keller (23), reported his observations on a larger material in which 200 dogs were used. He produced lesions in or near the hypothalamus in 104, lesions in the midbrain in 35, in the pons and upper medulla in 35, and in the cerebellum in 25 animals. Of this operated group, erosions were present in only 11 cases, 8 of which showed transverse chiasmal and 3 pontile lesions. Hemorrhages without ulceration were observed in several other animals. In a control group of 150 dogs, autopsy disclosed characteristic ulcerations in 12 underfed, chronically infected animals. Although Keller concluded that the number of craters occurring after lesions of the anterior hypothalamus were greater than after injury to the pons, reference to the number of operations performed at each level indicates that there is no real difference in their incidence. He also makes the important observation that the instillation of a few drops of blood into the 3rd ventricle through the corpus callosum, not infrequently resulted in multiple gastric ulcerations, although nerve cells had not been directly damaged. In the great majority of his operations, the third ventricle had probably been entered. It must be borne in mind, because of the relative inaccessibility of the hypothalamus, any surgical approach to this structure will of necessity cause considerable disruption of adjacent nervous tissue. Watts and Fulton (24), in 1935, in an attempt to produce hypothalamic lesions in the monkey, made a large bone flap, cut through the corpus callosum, entered the 3rd ventricle from above and destroyed its floor with either a blunt probe, by suction or electrocoagulation. Some of these animals had had previous removals of brain tissue. In 5 animals, they were able to induce erosions after such a destruction of hypothalamic tissue and several of these showed in addition a hemiparesis or hemianopsia, indicating that the damage was not confined to the hypothalamus. In each case, the lateral and 3rd ventricles had been entered, and in some a blood clot was found in the third ventricle. Another animal had been subjected to a midthoracic transection of the spinal cord and had received daily doses of epinephrine; subsequent examination showed the erosions.

Hoff and Sheehan (25) (by the subtemporal approach) produced with a bent probe a lesion in the hypothalamus. In 5 monkeys out of 19, erosions were found, but it is significant that in several of these cases epinephrine (a drug which is capable of inducing erosions) was given.

Martin and Schenedorf (26), in 1938, recorded their observations on hypothalamic lesions in a series of 40 cats and 7 monkeys. They found it very difficult to evaluate the results of "open" operations in small animals and resorted to the Horsley-Clarke stereotaxic apparatus for the production of focal lesions, without incising the dura. The size of their lesions was precisely controlled by employing a given milliamperage for a given period of time. Some lesions were made in the midline, others bilaterally. They succeeded in exploring the entire hypothalamic area and in producing almost identical lesions in different animals. In all of the

monkeys and in a large number of cats, the lesion was placed in the tuber cinereum to duplicate, if possible, the results of Hoff and Sheehan. In most cases the animal was acting normally within 36 hours after the operation. No changes were observed in gastrointestinal function. There was no vomiting of bloody fluid, no change in motility, no alterations of the free and total acid in the gastric contents, and no blood in the gastric juice. The stools were examined and showed no abnormality. The authors concluded that their results confirmed those of Magoun, Ranson and Hetherington (20) who found that mucosal alterations could not be produced in the digestive tracts of cats or monkeys by small, isolated, specifically located lesions in the hypothalamus.

At this point it may be recalled that during this period of extensive work on the hypothalamus the cerebral cortex and subcortex had been only infrequently used as points of attack for the solution of this problem. Schiff (6) made various lesions in the cerebral cortex, but was unable to produce gastric mucosal ulcerations, while Brown-Sequard (5) coagulated the cerebral cortex and produced gastric ulcerations. In more recent years cortico-autonomic interrelationships, bearing on this problem, have come into wide discussion. Several observers have obtained changes in gastric and intestinal motility, even to the point of intussusception, following the stimulation of the premotor cortex (27). In these experiments there was some question of spread of current to the hypothalamus. However, Mettler et al (28), in 1936, were able to produce multiple erosions in animals in which there was no disturbance of the hypothalamus, and only very small injuries to areas of the frontal lobe. He also induced ulcerations on removing the left occipital, parietal and temporal lobes in one operation, and following this 7 days later by amputation of the left frontal lobe. As far as could be determined clinically, the gastric manifestations appeared only after the second operation. Ulcers developed directly after bilateral ablation of the frontal poles, but did not occur when only the left frontal pole was ablated, first appearing after the right frontal lobe was extirpated at a second operation. Not without significance is Mettler's observation (29) that reticulocytosis developed in animals after careful removal of frontal cerebral cortex with preservation of the subcortex. There was little response in animals subjected to occipital lobe removals, but counts as high as 7.1% were found after ablation of frontal lobe tissue. In all of the animals with lesions of the frontal lobes, reticulocytosis began as an immediate response and reached its maximum in 4 days. This was associated with a sharp drop in the erythrocyte count although bleeding during the operation had been insignificant. These blood changes indicate the occurrence of an acute hemorrhage, possibly into the gastrointestinal tract. Mettler also found an increase of gastric acidity after destruction of frontal lobe tissue.

Fulton (30), in commenting on the review of gastrointestinal regulation and hypothalamic function by Sheehan, and on the article on the frontal lobe and gastrointestinal disturbances by Sweet (31), said that he had seen similar gastrointestinal lesions following bilateral simultaneous removals of the frontal lobes.

### The Peripheral Nervous System in Relation to the Erosions

To round out the discussion of the probable cause of the erosions, a brief review of the available data on the role played by the disturbances of the peripheral nervous system in this condition is warranted. The reports are conflicting and seem to indicate that a great variety of lesions, irritative or destructive in character, in one or another of the peripheral nerves have at various times been held responsible for the production of the erosions. Ebstein (7) obtained such erosions on sectioning the sciatic nerve and stimulating its central end. Similar results followed damage to the labyrinths and internal ear. Other observers have confined their experiments to the peripheral autonomic innervation of the stomach and other parts of the upper gastrointestinal tract.

The difficulty in interpreting the results of such experiments is apparently due to the great difference in the susceptibility of different experimental animals to the measures employed in the production of stigmata. Thus, the rabbit is the only laboratory animal which regularly shows ulcerations in a quota of cases subjected to vagotomy. Kobayashi (1) was able to produce stigmata in rabbits by ligation of one or both vagi at the cardia. Noteworthy is the observation that ligation of the left vagus resulted in the appearance of the typical lesions on the anterior wall of the stomach, while similar treatment of the right vagus caused them to form on the posterior wall. While other observers have been able to confirm the relationship of vagotomy to gastric ulceration in the rabbit, the results of similar experiments in other experimental animals have been for the most part negative (32). Tahna (33), in 1890, was able to obtain erosions following prolonged stimulation of the left vagus. Keppich (34) placed electrodes about the vagi and brought the wires out externally; electrical stimulation over an extended period resulted in gastric ulceration in a very large number of cases. Stahnke (35) attempted to stimulate the vagi by passing electrodes down by way of the esophagus to the cardia. He was able to produce erosions in only 2 dogs. Other investigators (Best and Orator, (36), Ettinger *et al* (37), Manning *et al* (38)), were able to induce erosions following prolonged electrical or other forms of stimulation to the vagus.

In similar experiments on the sympathetic nerve supply to the upper gastrointestinal tract, the resultant lesion has been mainly destructive in character. The exceptions are: the stigmata obtained by Kobayashi (1) following repeated pricking of the celiac ganglion, and the failure of Vischer (32) to provoke ulcerations in the dog by continuous stimulation of the splanchnic nerve over a period of 3 weeks. Celiac ganglionectomy carried out by Pincus (39), Popielski (40), and Kobayashi (1) has been the most effective in the production of erosions and bloody diarrhea. The added removal of the superior and inferior mesenteric ganglia seems to enhance the effect (4). Surgical lesions induced in the peripheral nerve trunks, however, have been much less effectual, producing only a few positive results (42). Erosions have been reported following bilateral adrenalectomy (43) (44). It is rather significant that the destruction of both sympathetic and parasympathetic innervation to the stomach usually fails to cause the development of ulcerations (33). Keller (45) found that bilateral vagotomy, performed



before placing a lesion in the hypothalamus, was effective in preventing the development of ulcerations. Vagotomy, however, did not protect his animals from gastric hemorrhage. Sympathectomy performed prior to hypothalamic injury apparently blocked the hemorrhages, but not the erosions. This led Keller to conclude that hemorrhages and erosions were the result of different mechanisms. The sharp line of demarcation between hemorrhage and crater formation has not been considered convincing by other authors (30).

Therefore, there is reason to assume that hemorrhagic and ulcerative processes are the result of disturbances of both sympathetic and parasympathetic innervation of the stomach. The concept of a constant conflict between these two divisions of the autonomic nervous system is not supported by experimental observations. As pointed out by Alvarez (46), there is little antagonism between the vagus and the sympathetic nerves in their control over the digestive system, both appear to function mainly as restrainers of activity.

*Comment.* It seems that the available experimental data indicate that lesions made at many different levels of the central nervous system and of the peripheral nerves may provoke the production of erosions. There are, however, inadequacies and difficulties in evaluating the earlier experimental work on the hypothalamus. It is significant, however, to note that the most precise placement of lesions in the hypothalamus has been unassociated with any gastrointestinal disturbances. On the other hand, massive or bilateral removals of cerebral cortex, although they did not involve the hypothalamus or its descending pathways, have resulted in the formation of erosions.

#### Clinical Observations Recorded in the Literature

Cushing (15), in support of his thesis, selected 11 cases from his own material, which are briefly summarized in the accompanying table (table I).

In all of the above listed cases in which multiple erosions or acute perforations were found at autopsy, there was hemorrhage into the gastrointestinal tract or peritonitis which clearly indicates the antemortem nature of the pathological process. The intracranial lesions were, in the majority of cases, tumors of the posterior fossa, or else involved portions of the cerebral hemispheres. In none of them can it be said that the hypothalamus was directly involved.

Next in order are the cases of Masten and Bunts (47) which were offered with the purpose of confirming the hypothesis of Cushing that these lesions are associated with a pathologic process involving the interbrain. The location and nature of the intracranial disturbance in their cases is shown in the appended Table (table II).

Here also, the tumors were either very extensive or else caused an obstructive hydrocephalus. Moreover, the cases in which meningitis or subarachnoid hemorrhage were present, can certainly not be used in support of the thesis of local pathology in the diencephalon. In none of the descriptions is mention made of the hypothalamus.

Strassman (48) surveyed a large group of cases to determine the relationship of intracranial lesions to multiple erosions and perforations. He introduces his report with the following statement:

"It is the generally accepted opinion that these ulcers follow certain intracranial processes which cause a state of parasympathetic irritation or sympathetic paralysis of autonomic centers in the hypothalamus."

But his large series, consisting of 26 cases of multiple erosions and 30 cases of acute perforations of the esophagus, stomach and duodenum, obtained as it

TABLE I

CENTRAL NERVOUS SYSTEM LESION	OPERATION	GASTROINTESTINAL LESION
1) Malignant nephrosclerosis with choked discs	None	Multiple erosions
6) Cerebellar astrocytoma	Suboccipital craniectomy followed by meningitis	Multiple erosions
3) Olfactory groove meningioma	Partial removal. Occlusion of both anterior cerebral, and one middle cerebral artery	Multiple erosions
4) Right cerebellar tumor	Suboccipital craniectomy with removal	Multiple perforations of stomach with peritonitis
5) Right parietal metastatic hypernephroma	Removal	Multiple perforations of the esophagus. Gastro-malacia.
6) Cerebellar tumor	Suboccipital craniectomy. Partial removal	Perforation of the esophagus.
7) Midline cerebellar tumor	Suboccipital craniectomy. Partial removal	Perforation of the esophagus.
8) Malignant nephrosclerosis with choked discs	None	Perforation of the stomach
9) Large aneurysm of the basilar artery	Suboccipital craniectomy	Extreme esophago-gastro-malacia.
10) Midline cerebellar tumor	Suboccipital craniectomy. Radiotherapy for 2 years.	Chronic duodenal ulcer.
(1) Tumor of 3rd ventricle	None	Duodenal ulcer.

TABLE II

LOCATION OF LESION	NATURE OF LESION
1) Left Frontal Lobe	Abscess with Terminal Meningitis
2) Corpus Callosum	Tumor
3) Thalamus, Lenticular Nucleus Internal Capsule, Lateral Ventricle	Hemorrhage
4) Basal Ganglia and Upper Brain Stem	Tumor
5) Cerebellum	Tumor
6) Subarachnoid Space	Meningitis
7) Disseminated	Encephalitis

was from patients who died in a mental institution and those autopsied by the New York Medical Examiner did not contribute much to support his contention. He concluded that the small hemorrhages of the gastrointestinal tract present in autopsy material under varying conditions, were agonal, and of no significance. When gross bleeding into the lumen of the gastrointestinal tract took place in

the absence of erosions, 9 out of 24 cases were found to have severe intracranial disorders. Of 26 cases in which multiple erosions were present, almost all showed well marked cerebral disease. Of 30 cases with acute perforations, only 3 did not show intracranial disease. Not a single case was of a solitary circumscribed lesion in the hypothalamus.

The most important feature of this series is the disseminated character of the disease in the central nervous system. The majority of gastrointestinal disturbances was present in patients with cerebral arteriosclerosis and superimposed encephalomalacia. The second most common cause was found to be fracture of the skull with subdural and subarachnoid hemorrhage and cerebral laceration. Of the 30 cases in which there occurred a perforation of the gut, over half suffered extensive trauma to the head with severe brain laceration. In decreasing frequency were spontaneous subarachnoid hemorrhage, acute meningitis and barbiturate poisoning. Two cases could not be linked with any neurological disturbance, and in one, the perforation took place following fracture of the cervical spine with cord compression.

The report permits of the conclusion that with increasing severity of the hemorrhagic-ulcerative process in the upper alimentary canal, the frequency of their occurrence in relation to a severe neurological disorder rises sharply. The most common form of damage to the brain was either traumatic or arteriosclerotic with softening. These observations also indicate that the gastrointestinal lesions cannot be traced directly to hypothalamic injuries. Other observers have noted the relationship between erosions and trauma to the central nervous system (49).

Recently, Staemmler (50) studied a group of neurological and neurosurgical necropsy cases in search of multiple erosions of the stomach and duodenum. Ten of 36 patients with acute and fatal disease of the brain showed the characteristic lesions. The majority of cerebral disturbances was generalized, in the nature of encephalitis, meningitis, or brain tumors subjected to surgery.

It seems that the observations discussed so far pointed to an extensive, diffuse or disseminated process involving the nervous system which was an etiologic factor in the causation of the erosions. The question as to whether relatively isolated lesions of the central nervous system can similarly cause formation of stigmata is more difficult to answer, mainly because of the failure of disease processes to remain confined to a definite structure or small areas. Furthermore, intracranial vascular and fluid imbalances may produce additional disturbances.

Moolten (51) recorded the case of a boy, aged 16 years, who, while diving, suffered a compression fracture of the 5th and 6th cervical vertebrae. Although there was some return of power and sensation in the arms, the legs remained completely paralyzed and anesthesia was present below the 3rd thoracic segment. On the 4th day after the accident he began to complain of abdominal pain and vomited repeatedly, and on the 16th day he passed a tarry stool. He died on the following day.

Postmortem examination disclosed a crushed spinal cord at C5-6. The gastrointestinal tract was filled with blood and an ulcer with a bleeding vessel at its center was disclosed in the duodenum. The hemorrhage was considered to be the cause of death.

*Comment.* This case is of significance because of the appearance of massive gastrointestinal bleeding from an ulcer in close association with a transverse lesion of the spinal cord. The ulcer was described as "subacute," but the age of the patient, the previous negative history, and the rapid development of abdominal pain on the 4th day after injury, all indicate that the hemorrhage was the result of a recent and rapidly developing process.

Nitsche and Suckle (52) reported a case of a man, aged 64 years, who presented signs and symptoms diagnosed as those of a cerebellopontile angle tumor. A preoperative gastrointestinal X-ray series was negative and a gastric analysis showed no free acid. A left suboccipital craniectomy was performed with the intracapsular removal of a typical acoustic neuroma. The patient convalesced satisfactorily until the 5th postoperative day when he became drowsy. He passed a tarry stool on the 9th day. There was no vomiting, no abdominal discomfort and no abnormal physical findings. Shortly thereafter, the patient passed into a state of collapse and died. At post mortem examination, a foul peritonitis was found. A perforation, about 1 cm in diameter was found in the first portion of the duodenum; the edge of the ulcer showed a fibrino-purulent exudate. Examination of the brain revealed no hemorrhage or softening of the medulla. There was distortion of the left side of the 4th ventricle in conformity with the overlying hemorrhagic mass in the cerebellopontile angle.

*Comment.* It is significant that observations were recorded in this case pointing to the absence of papilledema and to the normal size of the ventricles. The diencephalon was found to be unaffected.

Mossberger (53) reported a case of a 5 day old infant who suddenly passed into a state of shock and died. At postmortem examination, an acute peritonitis was disclosed, and an acute punched-cut perforation of the duodenum. The ulcer edge showed almost complete absence of an inflammatory reaction. The only other abnormality was a pink, globular nodule, 3 mm in diameter, arising from the undersurface of the hypothalamus which had produced considerable disruption of the structures in the tuberal region. It was diagnosed as a hamartoma.

*Comment.* This is the only instance in which a circumscribed lesion was found in the tuberal portion of the hypothalamus. Unfortunately, the history is incomplete.

Sweet et al (32) recorded a case of special significance. In this instance, a well circumscribed lesion above the diencephalon was apparently instrumental in the production of multiple erosions and a massive gastrointestinal hemorrhage.

A woman, aged 47 years, had intractable pain in the face. Since nerve blocks and nerve section gave her no relief, a bilateral prefrontal lobotomy was performed. The incision was made 3 cm behind the orbit and 6 cm above the superior border of the zygomatic arch. The ventricle was entered on each side, but no bleeding was encountered. Immediately following the operation she was alert and oriented, and continued to do well for the first week, except for a rise in temperature to 102° F, and some lower abdominal pain. Because of bilateral thrombophlebitis and a pulmonary infarct, the common femoral veins were exposed and sucked out. Despite the small amount of blood lost, her blood pressure dropped to 60 systolic and 40 diastolic, and she became stuporous. On the



11th day, a 1% reticulocytosis was noted. On the 14th day her hemoglobin was 9.5 gm. On the 15th day she passed massive tarry stools. She was transfused with some improvement. On the 28th day, her condition became poor, and for the 4 subsequent days her blood pressure was at shock levels. Stools showed a 4 plus guaiac test. Her course was also associated with hyperchloremia, hypernatremia, and azotemia.

Postmortem examination disclosed a dark-red lacerated lining of the esophagus, which microscopically showed a necrotic mucosa with occasional ulcerations reaching the muscularis. The adjacent lining was heavily infiltrated with round cells. The remainder of the alimentary canal was normal, except for similar ulcerations of the rectum. There were multiple infarcts of the lungs.

The brain was sectioned in the sagittal plane. The lobotomy incisions were represented by non-hemorrhagic slits passing through the ventricular tip, but not involving the basal ganglia. Practically all the fibres were divided. Microscopic examination of the nuclei of the basal ganglia disclosed no significant changes.

*Comment.* Of the four foregoing case reports, three indicated the coexistence of fatal gastrointestinal hemorrhage with widely separated lesions in the central nervous system. In the fourth case, the relative effects of a lobotomy and those of pulmonary embolization on the production of the gastrointestinal lesions are difficult to evaluate.

#### OUR OWN MATERIAL

*Case 1 (P.M. 14294)—Guillain-Barré syndrome with massive fatal hematemeses from multiple gastric erosions.*

A man, aged 66 years, was brought to the Mount Sinai Hospital with a history of repeated attacks of fainting, considered to be a manifestation of Stokes-Adams syndrome. Two weeks prior to his admission, he experienced paresthesias in his hands with inability to distinguish heat from cold. He complained of weakness. Neurological examination was at first negative. The weakness persisted, and on the 5th hospital day, he suddenly collapsed. The deep tendon reflexes were then found to be hypoactive, and shortly thereafter, a right lateral rectus paresis appeared. This was soon followed by marked weakness of the extremities, inability to cough and difficulty in articulating. Vibration and position sense were impaired up to the knees and hypalgesia was intermittently present. The abdominal reflexes were absent. There were no pathological reflexes. A lumbar puncture disclosed a total protein of 740 mg per cent, and 6-8 small round cells per Cu. mm. The impression was that of a Guillain-Barré syndrome. The patient grew weaker, and experienced great difficulty with breathing. The intercostal muscles became involved, and with this, cyanosis developed. He was placed in a respirator. At this time, the patient vomited some coffee-grounds material. Several hours later there was a massive hematemeses. A tube was passed and several hundred cc. of black fluid were withdrawn. Shortly thereafter, the patient died.

*Postmortem Findings.* The distended stomach showed many round to oval ulcerations of the stomach, 3-10 mm in diameter, 1 mm in depth, and mostly on its posterior wall. There were several similar erosions in the duodenum. The lumen of the small bowel was filled with a considerable amount of black material. The lungs were negative. The cause of death was attributed to the massive gastrointestinal hemorrhage. The lower segments of the spinal cord, and the peripheral nerves were not available for examination. Sections of the cervical spinal cord, medulla oblongata, pons, midbrain, and subcortex disclosed no demyelination and no abnormality other than a diffuse increase in the number of oligodendroglia.

*Comment.* The significance of this case lies in the fact that the brain disclosed no focal disease and only a few alterations on microscopic examination. The latter were of little clinical importance as they are not infrequently encountered in relatively normal brains. In this case, multiple erosions with fatal hemorrhage probably occurred from disease of the lower segments of the central and/or components of the peripheral nervous system without any implication of the brain.

*Case 2 (P.M. 13703)—Herniated intervertebral disc at the cervical 6-7 interspace. Death several days postoperatively from a cervico-thoracic hematomyelia. Vomiting of altered blood.*

A man, aged 37 years, was brought to the Mount Sinai Hospital with a history of difficulty in walking and voiding. Examination disclosed a spastic quadraparesis, a bilateral Babinski sign, and an apparent sensory level at the seventh cervical dermatome. Myelography revealed a defect at the fifth cervical vertebra, suggestive of a tumor. A cervical laminectomy was performed under local anesthesia and supplemented by pentothal, and an extruded disc was found at the 6th-7th interspace. A portion of the disc was removed on the left side. At the termination of this procedure, it was noticed that the patient was not using his intercostal muscles and was unable to move his extremities. His temperature rose rapidly to 104.5° F. He was placed in a respirator and subjected to frequent intratracheal suctioning. On the 2nd day after the operation, he vomited a large amount of dark colored material, continued to vomit frequently, and his abdomen became distended. The following day, hemorrhagic fluid was withdrawn from his stomach through a Levin tube. Later in the day, his temperature rose to 107° F., and he died.

*Postmortem Examination.* The esophagus was normal. The stomach was markedly congested with many small scattered erosions. In addition there were two punched-out ulcerations with blackened floors in the antrum of the stomach, measuring 1.5 cm in diameter. There were some pulmonary edema and atelectasis. The brain was normal. The spinal cord was the site of a hematomyelia, extending from the upper cervical to the midthoracic segments; it was most marked in the lower cervical region. There was secondary ascending and descending degeneration.

*Comment.* In this case again, the brain was entirely free of pathologic alterations. Thus, no portion of this organ can be held responsible for the gastric manifestations. The spinal cord, however, revealed a vast destructive lesion affecting the cervical and upper thoracic segments.

*Case 3 (P.M. 14496)—Cerebellar hemorrhage; three days of coma leading to death. Vomiting of altered blood during the first and second days.*

A nurse, aged 68 years, was brought to the Mount Sinai Hospital in a state of coma. On the morning of admission, she experienced severe nausea, dizziness and headache, and passed rapidly into a state of stupor. Her face was asymmetric, and the extremities, especially the right, were flaccid. During the examination, she repeatedly vomited bloody material. The vomiting continued during the second day, but ceased on the day of her death. Her blood pressure was maintained at about 135 systolic and 70 diastolic until the last few hours of life. There was no history of hypertension or diabetes.

*Postmortem Examination.* The esophagus was normal. The stomach was dilated and contained 500 cc of brownish-green fluid. The mucosa showed several irregular dark erosions in the prepyloric region. The largest erosion was elliptical and measured 1.5 cm. The brain showed some organized blood clot in the cisterna magna. A large hemorrhagic mass was found in the left cerebellar hemisphere (fig. 1), completely replacing the dentate nucleus and the structures medial to it. The hemorrhage extended into the 4th ventricle and a small amount of blood was present in the 3rd and lateral ventricles.

*Comment.* In this instance, there is a massive hemorrhagic lesion in the left cerebellar hemisphere with a small amount of blood escaping into the ventricular system as high as the lateral ventricles. There was an extensive implication of the lower brain stem with the main destructive process in the cerebellum. The attempt in this instance to identify a well circumscribed focus responsible for the gastric lesions, would be hazardous.

*Case 4 (Surg. 47338)—Hemangioendothelioma of the superior portion of the left cerebellar hemisphere with an almost fatal gastrointestinal hemorrhage on the 4th day after its removal.*

A boy, aged  $3\frac{1}{2}$  years, was brought to the Mount Sinai Hospital two weeks after the onset of an illness marked by unsteady gait, infrequent bouts of vomiting and headache. Papilledema was present. A midline cerebellar tumor was diagnosed, and a suboccipital craniectomy was performed under endotracheal anesthesia without apparent shock. The superior portion of the left cerebellar hemisphere, containing an olive sized tumor, was removed. During the operation a ventricular puncture was performed through a right occipital burr hole. It disclosed ventricles of normal size, and the cerebrospinal fluid under increased pressure. The patient's condition after the operation was good; he was alert, his blood pressure was well maintained, but his temperature rose to  $103^{\circ}$  F. On the 4th postoperative day he became lethargic, and there was an episode of transitory cyanosis, followed by vertical and rotatory nystagmus, deviation of the eyes to the left, and clonic movements and spasticity of the left arm. A posterior fossa hematoma was considered. A ventricular puncture was unsuccessful, and a lumbar puncture revealed moderately



FIG. 1. Coronal section of the cerebellum, showing the massive hemorrhage into the left cerebellar hemisphere and the 4th ventricle (see text for clinical details).

bloody fluid under slightly increased pressure. That night, the patient began to vomit "coffee-grounds" material, and his abdomen became distended. Gastric suction was begun and he was transfused. He passed a tarry stool. His hemoglobin was 90 per cent, and he appeared to be dehydrated. On the 6th postoperative day he passed several tarry stools containing red blood clots, and he continued to vomit coffee-grounds material. The blood pressure fell to 60 systolic and 40 diastolic. He was transfused and his blood pressure rose to a normal level. On the 8th day, stools contained no fresh blood, but were still dark. On the 11th day, the stools were chemically free of blood. He continued to improve and was discharged on the 17th day after operation.

*Comment.* In this case, a rather small vascular tumor (hemangioendothelioma) in the left cerebellar hemisphere, unaccompanied by a detectable enlargement of the ventricular system, did not apparently cause any recognizable disturbance of supra-tentorial structures, including the hypothalamus.

*Case 5 (P.M. 14502).—Small right frontal glioma; two days of coma leading to death. No*



*significant increase of intracranial pressure, massive cerebral edema or distortion of the ventricular system. Vomiting of altered blood concomitant with the onset of coma.*

A man, aged 71 years, was brought to the Mount Sinai Hospital with the history that, for one week before his admission, he had been unusually drowsy; for the last 4½ hours he had become irrational; two and one half hours later he had a generalized convulsion, passed into coma, and vomited "coffee-grounds" material. Examination disclosed a left hemiparesis, including the face, and a left Babinski sign. A lumbar puncture yielded clear cerebrospinal fluid with an initial pressure of 200 mm of water. The protein was 56 mg. per cent. During the first day in the hospital, while his blood pressure was well maintained, he vom-



FIG. 2. Coronal sections of the brain, showing the location of an ependymoma in the right frontal lobe, rostral to the anterior horn of the lateral ventricle without causing significant deformity. (Case 1, Table IV). (See text for clinical details).

ited about 1000 cc of altered blood. Thereafter, as he sunk deeper into coma, the vomiting ceased. Bronchopneumonia developed, and he died on the third day in the hospital.

*Postmortem Examination.* The distal esophagus was dilated, edematous, thickened, and the mucosa was necrotic. The mucous membrane was for the most part replaced by a tenacious covering of black, altered blood. The mucous lining exhibited numerous erosions, about 5 mm in diameter, covered by altered blood. The remainder of the bowel was filled with tarry, liquid stool. The brain was rather large, and the right frontal pole was somewhat bulging and more rounded than the left. A tumor mass was found in the right frontal area (fig. 2). It extended from the genu of the corpus callosum forward into the frontal pole. The neoplasm was grayish-pink in color and measured 3 cm in its largest diameter. It came



into contact with the tip of the right ventricle without causing any ventricular distortion or edema of the hemisphere posterior to the lesion. The tumor was histologically a transitional ependymoma.

*Comment.* In this case a well circumscribed expanding lesion was present in the fore-brain, but was situated quite a distance from the diencephalon and caused no direct or indirect changes in the hypothalamic region of the brain.

### A Survey of General Autopsy Material

The impression which links multiple ulcerations of the gastrointestinal tract with disturbances of the nervous system was originally based on only a few clinical case reports and on some experimental data. In recent years, a larger

TABLE III  
*Cases with Severe Local Disease*

DIAGNOSIS	P.M. NUMBER	NERVOUS SYSTEM INVOLVEMENT
1) Carcinoma of the lung; abdominal carcinomatosis	14535	Multiple cerebral metastases (craniotomy)
2) Carcinoma of the pancreas; abdominal carcinomatosis	13894	Hemangioma of the cerebellum (post-mortem discovery)
3) Carcinoma of the lung; abdominal carcinomatosis; peritonitis	13891	Multiple cerebral metastases
4) Appendectomy; peritonitis; paralytic ileus	13454	Multiple areas of softening
5) Malignant nephrosclerosis; sympathectomy with infarct of the kidney	14444	Removal of sympathetic chain
6) Perforated caecum; peritonitis	14088	None
7) Intussusception of bowel; peritonitis	14082	None
8) Hodgkin's disease; perforation of bowel; peritonitis	13729	None
9) Carcinoma of the breast; abdominal carcinomatosis	13562	None
10) Bronchiectasis; pneumonectomy; anoxic death	13826	None

number of such cases came under observation in which the nervous system was subjected to careful study. However, the material selected for such studies, consisted, in the main, only of those instances in which there was an obvious neurological or psychiatric disorder.

In the present study, an attempt is made to correct this defect by bringing under investigation a larger number of cases studied on the wards of The Mount Sinai Hospital, irrespective of whether the fatal illness fell into the categories of general medicine, neurology, or surgery. The material surveyed consisted of 544 cases which were observed during the 4 years of the post-war period, when investigations were more thorough and more fully recorded. Of the total number of these cases, 500 were excluded, mainly because they did not disclose any "stigmata" on postmortem examination, or in some the stigmata were found alongside a lesion intrinsic to the affected organ (esophagus, stomach and duodenum), such as a carcinoma, peptic ulcer or else formed a part of the status following a gastrointestinal operation.

Thus, there remain 44 cases (an incidence of 8%), in which typical multiple erosions were present. But among them, there were 10 cases in which there co-existed a disease process in the abdominal cavity. They included instances of Hodgkin's disease, metastatic carcinoma of regional lymph nodes, and peritonitis. It is obvious that under such conditions there are great difficulties in identifying

TABLE IV  
*Primary Fatal Disease of the Nervous System*  
A. Brain Tumors

LOCATION	P.M. NUMBER	CHARACTER OF THE LESION
1) Frontal lobe	14502	Ependymoma* (fig. 2)
2) Fronto-temporo-parietal	14095	Polar spongioblastoma (fig. 3)
3) Temporo-frontal	14187	Transitional glioneuroma (fig. 4)
4) Parieto-occipital	14353	Meningioma
5) Corpus callosum	13980	Ependymoma (fig. 5)
6) Cerebellum	13956	Hemangioendothelioma* (fig. 6)
7) Cerebellum	13677	Hemangioma (fig. 7)

B. Vascular Disease

LOCATION	P.M. NUMBER	CHARACTER OF THE LESION
1) Subdural and subarachnoid	13893	Hemorrhage
2) Disseminated	14267	Encephalomalacia
3) Disseminated	14403	Encephalomyelomalacia with atrophy
4) Cerebellum	14496	Hemorrhage
5) Cervical and thoracic spinal cord segments	13703	Hematomyelia

C. Inflammatory Disease

LOCATION	P.M. NUMBER	CHARACTER OF THE DISEASE
1) Disseminated	14387	Acute poliomyeloencephalitis
2) Spinal cord; spinal roots	14294	Guillain-Barré syndrome

D. Varia

LOCATION	P.M. NUMBER	CHARACTER OF THE DISEASE
1) Disseminated	14574	Post-measles encephalopathy
2) Cerebrum (of infant)	13391	Congenital malformation

\* Not operated.

the essential factors or estimating the role played by any one of them in the production of the erosions under investigation. Hence they were placed in a separate group (table III).

*Comment.* The presence of local disease in the abdomen makes it difficult, if not impossible, to assess the relative importance of local pressure, vascular

dysfunction, or involvement of peripheral nervous components as contributing factors in the formation of multiple erosions. It is not without significance, however, that over half of the cases in Table III show, in addition to local intra

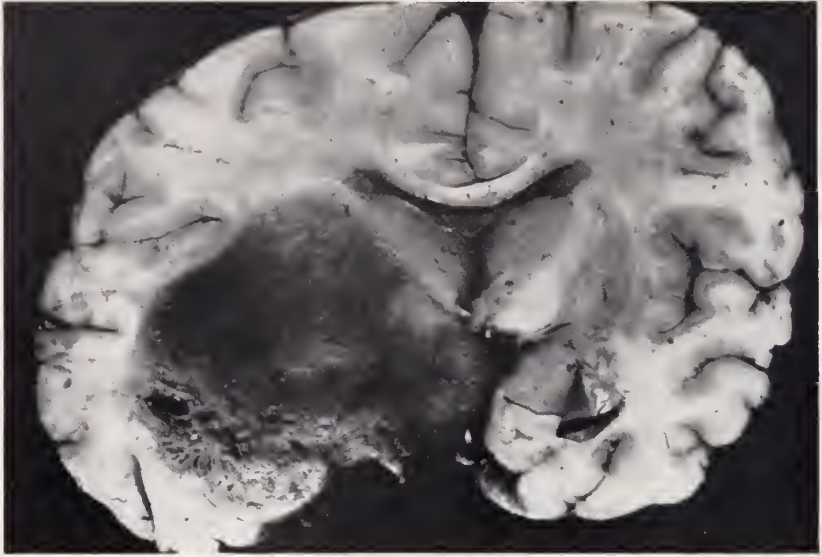


FIG. 3. Coronal section of the brain, showing a large infiltrating tumor (Spongioblastoma) in the temporal lobe (Case 2, Table IV).

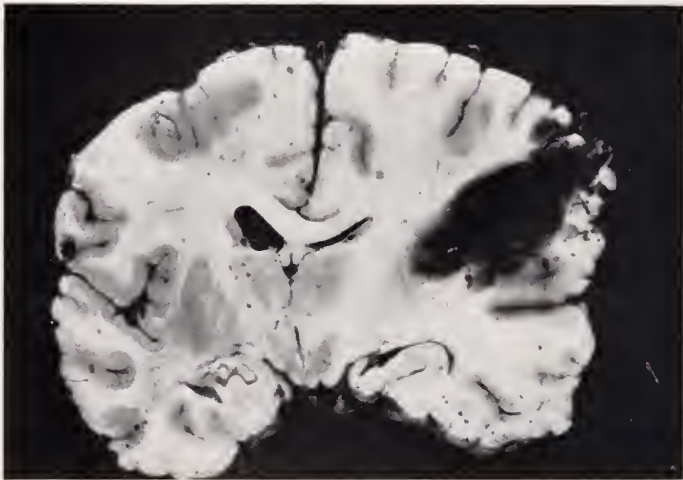


FIG. 4. Coronal section of the brain, showing part of the tumor in the parietal lobe. (Case 3, Table IV).

abdominal disease, a substantial disturbance in the central or autonomic divisions of the nervous system.

The remaining 34 cases, in which there were no local disease conditions in the

abdomen, aside from the erosions, were investigated with special attention to the presence and localization of pathologic alterations in the central nervous

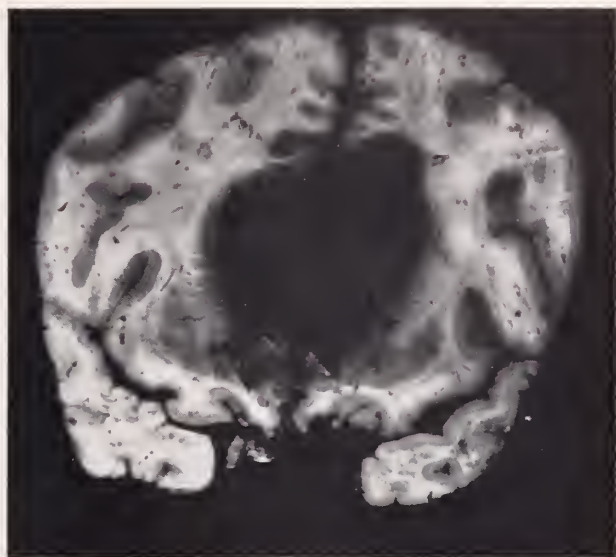


FIG. 5. Coronal section of the brain, showing an ependymoma in the Corpus Callosum (Case 5, Table IV).

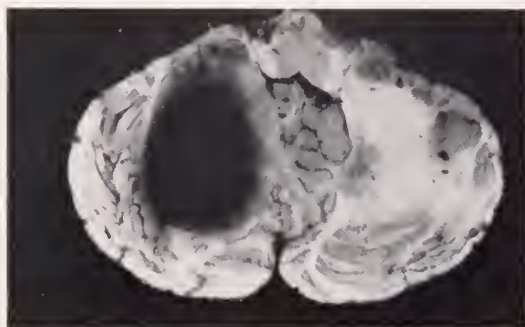


FIG. 6. Coronal section of the cerebellum, showing the site of the tumor (Case 6, Table IV).

system. For reasons of convenience they were distributed into the following four subgroups:

- 1) Primary fatal disease of the nervous system (table IV);
- 2) Secondary disease of the nervous system, materially contributing to the fatal outcome (table V);
- 3) Clinical evidence of severe involvement of the nervous system with only mild diffuse neuropathological changes, or none demonstrable (table VI);
- 4) No clinical or pathological manifestations of disease of the nervous system (table VII).



*Comment.* The cases assembled in Table IV under the heading of primary nervous system disease, indicate how great the variety of type and location of



FIG. 7. Coronal section of the cerebellum, showing the tumor projecting into the 4th ventricle (Case 7, Table IV).

TABLE V

*Secondary Disease of the Nervous System, Materially Contributing to the Fatal Outcome*  
Vascular Disturbances

LOCATION	P.M. NUMBER	CHARACTER OF LESION	PRIMARY SYSTEMIC DISEASE
1) Subdural	14538	Hematoma	Cardiac failure
2) Subdural; intracerebral; intracerebellar	13684	Hemorrhage	Leukemia
3) Subdural; subarachnoid	13383	Hemorrhage	Hemorrhagic disease of the newborn
4) Disseminated; intracere- bral; intraspinal	14481	Hemorrhage; ma- lacia	Aplastic anemia
5) Disseminated: intracere- bral	14200	Encephalomalacia	Leukemia
6) Subarachnoid; intracere- bral; mesencephalic	13833	Hemorrhage	Malignant nephrosclerosis
7) Increased intracranial pressure	14008	Idiopathic	Malignant nephrosclerosis
8) Subdural; mesencephalic pontine	14273	Hemorrhage	Subacute bacterial endo- carditis

the lesions can be, to result in multiple erosions of the esophagus, stomach and duodenum. Thus, it can be said that no isolated part of the nervous system can be regarded as the seat of the disorder causing these erosions. It may be added

that even brain tumors cannot be considered as locally restricted since the majority of such lesions is complicated by the accompanying increased intracranial pressure, a shift of the cerebral structures, or by the disturbances occasioned by surgical intervention.

*Comment.* In the series listed in Table V, in almost all of the cases in which the central nervous system was secondarily involved, there was a hemorrhagic diathesis or disease of the blood vessels. The accompanying intracranial disorder was also in the nature of a hemorrhage or increased intracranial pressure.

TABLE VI

*Clinical Evidence of Severe Involvement of the Nervous System with only Mild Diffuse Neuropathological Changes or None Demonstrable*

CLINICAL MANIFESTATIONS	P.M. NUMBER	PATHOLOGICAL FINDINGS
1) Sudden coma, Jacksonian seizures, signs of a focal cerebrovascular accident	14100	Mild chronic vascular encephalopathy; symmetrical hydrocephalus (died after one day of illness)
2) Generalized convulsions, followed by shock	14152	Normal brain (died on 2nd day of life)
3) Convulsive disorder (considered to be subdural hematoma)	13346	Gliososis and satellitosis
4) Lethargy, incontinence, oculomotor paresis, hyperpyrexia, coma	13757	Trichinosis; brain normal
5) Organic mental syndrome, hallucinations	14305	Acute disseminated lupus erythematosus; diffuse degenerative encephalopathy

*Comment.* All of the cases in Table VI presented a clinical picture of a severe disturbance of neuronal function. In 2 cases, the fatal outcome occurred so rapidly that there may not have been time for the development of demonstrable neuropathologic changes.

TABLE VII

*Cases Free of Clinical or Pathological Manifestations of Disease of the Nervous System*

CAUSE OF DEATH	P.M. NUMBER
1) Myocardial infarction	13845
2) " "	14571
3) Pulmonary infarction	14385
4) Myocardial and pulmonary infarction	14471
5) Pentothal anesthesia (death during induction)	13962

*Comment.* It may be of significance that in 4 of the 5 cases in this table, not associated with clinical evidence of nervous system disturbance, there were infarctions of the heart or lung. Such pathologic states are usually associated with the appearance of clammy skin, sweating and a shocklike state, indicating massive functional implication of the autonomic nervous components. This observa-

tion adds support to the view held by some observers that such shock, in which there is a massive sympathetic or parasympathetic discharge, is a likely basis for the formation of multiple erosions.

#### SUMMARY AND CONCLUSIONS

In the foregoing reinvestigation of the problem of multiple erosions, consideration was given to lesions occurring in the upper alimentary tract, which have well defined anatomico-pathologic features. The lesions in question are multiple, small, shallow ulcerations, limited to the mucosa and submucosa, most often found in the stomach and upper part of the duodenum and lower part of the esophagus, and less frequently encountered in other parts of the alimentary canal. These ulcerations display vascular congestion, dilatation, and sometimes thrombosis and hemorrhage with a cellular reaction at their periphery (indicating their antemortem origin). Acute perforations, or so-called "blowouts" of the wall of the gut were also included in this analysis for they too may be caused by a disorder of the nervous system. The clinical manifestations of these lesions were briefly discussed and mention was made of "black vomit" as an ominous feature, most commonly encountered in patients with clinical evidence of nervous system disease, but also during a rather unsatisfactory postoperative course or in preterminal systemic disorders.

In general, this investigation, as already indicated, was undertaken primarily to find an adequate answer to the following questions:

- 1) Does some dysfunction (organic or otherwise) of the nervous system provoke the formation of the lesions in question?
- 2) Can any special disease form of the nervous system be held responsible for the erosions?
- 3) Can a relatively isolated lesion, irrespective of its character or location, be responsible for the hemorrhagic or non-hemorrhagic erosions in the upper alimentary tract?
- 4) Are such lesions confined to a certain portion of the nervous system, and if so, is the hypothalamus the area of predilection?

A review of the literature yielded significant information, which serves to answer in part the questions posed. Almost all authors reporting on multiple erosions of the gastrointestinal tract have recognized the role played by the nervous system in their production. Some evidence was found in other acute ulcerations of the upper gastrointestinal tract, such as in the Curling's ulcer resulting from severe burns, that the nervous system may also be drawn into the pathological orbit. Moreover, the experimental work on a number of laboratory animals clearly indicates that multiple erosions, perforations, and hemorrhages can be readily produced by disruptive changes in parts of the central or peripheral nervous system.

Ulcerations with or without hemorrhages are not the result of any specific neurological disease, whether local, diffuse, or disseminated. They are encountered in disorders of the nervous system caused by trauma, infection, hemorrhage, tumor, toxic factors or congenital malformations. They are present most

commonly when the affliction of the nervous system is extensive. However, some recorded cases show that these acute gastrointestinal lesions may accompany relatively isolated disease processes either in the spinal cord or brain. These observations, together with the available experimental data, favor the conclusion that discrete lesions occurring at almost any major level of the brain, spinal cord and peripheral and autonomic nerves can be instrumental in the production of the gastrointestinal lesions under consideration. This serves to explain why widespread disorders of the nervous system are most frequently found in conjunction with the "stigmata."

The concept that the hypothalamus is the site of predilection for the causation of the erosions finds no adequate support in recorded and well studied material.

An analysis of our own material disclosed evidence which is in accord with the foregoing conclusions. Five cases were selected from the scrutinized material in which the erosions were associated with lesions in the nervous system which were quite circumscribed. These cases served to show that no single segment of the cerebrospinal axis need be considered as the only one capable of provoking the gastrointestinal lesions. Moreover, additional material (shown in the tables) indicates that diffuse damage to the brain is more likely to serve as a cause for the formation of these erosions.

A second step in this study was to investigate the frequency with which the erosions are encountered in general autopsy material and to correlate their occurrence with changes in the nervous system of the affected cases. The material used for this survey, collected over a period of 4 years, indicates that the frequency of erosions was about 8% in general autopsy material. Almost all of these cases, exclusive of those in which local factors were operative, showed some involvement of the nervous system, pathologically or clinically. Another important feature noted in our material was the presence of erosions in instances in which there was no indication of a nervous disorder during life, but which disclosed striking neuropathologic alterations at postmortem examination. In fact, such gastrointestinal erosions may serve as a pathological indication of nervous system involvement. Their discovery at autopsy examination should arouse strong suspicion of the existence of disease of the central or peripheral nervous systems.

It may, therefore, be concluded, that gastric erosions and similar lesions in other parts of the alimentary tract are traceable to a dysfunction of the nervous system. Widespread disorders in that system are most likely to produce these lesions, but, in a sense, the nervous system is "equipotential," as almost any region can be the focal point of development of the pathological process which may express itself in acute gastrointestinal ulcerations. Finally, no selective point in the central or peripheral nervous systems can be regarded as crucial for the formation of these lesions, and this is particularly true of the hypothalamus.

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## GASTROENTEROLOGY AS A SURGICAL SPECIALTY AT THE MOUNT SINAI HOSPITAL

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The Mount Sinai Hospital of New York City has become a center of interest for gastroenterology, medical and surgical. Without boasting, it is a fair statement to make that the profession of the country, or for that matter, the world over, look with expectation to the staff of this hospital when problems of a gastroenterological nature are up for discussion. Whether it be a medical topic relating to stomach or intestinal tract, or a question of surgical technic; whether it be the follow-up experience of surgical procedures, or scientific data from the laboratory, this hospital now takes its rank among those institutions which contribute weighty opinions on gastroenterological problems.

The beginnings and the rise of interest in this subject at Mount Sinai may well be justifiably attributed to Dr. A. A. Berg. Through his influence in the Medical Board and at his suggestion the first specialized clinic in gastroenterology was organized in the Out-Patient Department of the hospital; Dr. Edward A. Aronson was appointed Chief in 1913 serving in that capacity until his sudden demise in 1922. Under Dr. Aronson and his staff not only were careful clinical studies on cases referred from the other clinics amply presented, but clinical research was encouraged, group studies were made, meritorious papers written and published. The liason with the service of Dr. A. A. Berg was close and harmonious.

In 1920 a specialized service in Gastrointestinal surgery was recognized by the medical and lay boards of the hospital, much of the material background of such a service being attributable to the generosity of Mr. Clarence Winpflheimer a close friend and admirer of the talent and ability of Dr. Berg. The tablet which marked this generous gift was for years implanted in the wall of Ward M, which with Ward N and some beds in the surgical wards of the Children's Pavilion constituted the "G.I. Service" of the hospital. The routine biological chemistry, gastric, pancreatic and intestinal, was in the hands of Dr. Samuel Bookman, the bio-chemist; physiological research was brilliantly formulated by Dr. Eugene Klein.

Grand Rounds on Dr. Berg's Service was held on Sunday morning at ninety-three, the group congregated in the old Reception Ward downstairs, the surgical group headed by Dr. Berg, the medical contingent by Dr. Aronson. The first interest was devoted to the follow-up of surgically treated patients. The patients summoned by postal card by the capable sympathetic and ever-present secretary, Mrs. Bea Wile, were seated about the benches of the reception ward intermingled with emergency cases, new admissions and all the hub-bub that marked the routine of that vestibule to all the hospital's activities. One by one they were called into the inner room where stood (not sat) the group of physicians, the patient to be questioned, examined, weighed and his answers recorded. Dr. Mage was chief clerk of the files and his interest and honest scrutiny made



these records over the course of years of great value. Then, the operation of gastroenterostomy was the topic of chief interest and it constituted the routine operation for all benign gastric complaints, always when ulcer was present, frequently even when no ulcer could be determined. It should be recalled that radiography of the gastrointestinal tract was then in its infancy (1912-1916) and clinical experience and judgment and skill determined surgical course and therapy. Intestinal surgery except for carcinoma was almost non-existent, with an occasional appendicostomy or cecostomy for ulcerative colitis as two other exceptions.

When the follow-up cases had been disposed of, the entire group headed by Dr. Berg in his white coat, usually in conversation with the neat and tidy Aronson, tramped through the halls in one massive parade to make rounds on Wards M and N. By now it was 10:30 a.m. and the party was well warmed-up. It might be of interest to recall some of the personalities in the group, many of whom have long since passed away and many of whose very names have been forgotten by the younger staff members of the hospital. Dr. Aronson was an excellent clinician; he was the first physician at Mount Sinai to limit his practice to gastroenterology. He was a capable organizer, and a liberal and kindly head of his clinic, giving free rein to any man of his staff who had an idea and wanted clinical data to demonstrate his point. I was first assistant, sometimes conforming, often belligerent; then came Samuel J. Goldfarb, originally an obstetrician, now a gastroenterologist, later a roentgenologist; then little Samuel Weiskopf (now of Lebanon Hospital), Eddie Hollander, S. Winfield Kohn. A few years later Asher Winkelstein returned from his post-graduate studies in Germany, joined the group, later to achieve its medical leadership.

As Dr. Berg strode into Ward M a sudden hush overcame the ward; all activities ceased as his strident voice called upon the Head Nurse, Miss Rooney, to assure order and fall-in. Dr. Berg's chief of staff, associate surgeon, was Dr. Richard Lewisohn, whose independence of opinion and strictly critical judgment was of greatest value in helping to formulate clear and concise evaluations of indications and results. Dr. Paul Aschner was Adjunct Surgeon much of this time and capable and doughty in argument. The genial and quiet Eugene Klein with his remarkably scientific mind and approach to physiological viewpoints was an asset of inestimable value. Dr. A. O. Wilensky, a stormy petrel, was also much in evidence. Rounds progressed from bed to bed; the clock ticked on, the arguments were free and easy. Dr. Berg encouraged liberal discussion and welcomed suggestions; if a man had an idea and wished to study or follow an hypothesis, Dr. Berg was helpful and free-handed. The discussions were warm and marked by no formalism, absence of limiting conventionalities, and by cordial relationships between the invited participants. Rounds were usually only terminated by the advent of the lunch trays. One particular feature is always fresh in my memory. A survivor of a total gastrectomy was a rare case in those days; one such patient was frequently demonstrated at 12 noon those Sunday mornings when he was invited to lunch in the wards while we stood about and marveled that a man without his whole stomach could consume so large a meal.

In 1922 the first reports regarding the new operation of partial or sub-total gastrectomy reached this country. Dr. Lewisohn, on a visit to Innsbruck, had seen Von Haberer perform this marvel, this so-called extreme operation for the cure of peptic ulcer. Dr. Berg was immediately interested for the results of gastroenterostomy were becoming increasingly and evidently unsatisfactory and the rate of recurrent gastrojejunal ulcer was being emphasized by the Mount Sinai group to the discomfiture of the surgical profession outside. Most of the internists and surgeons were singularly content with that antiquated operation and refused to accept the criticism and the follow-up figures of Lewisohn, of Mage and Klein and others of the surgical profession abroad.

Dr. Berg's magnificent surgical technic and inventiveness and brave approach, his solicitous after-care of his patients, soon made the operation of subtotal gastrectomy a reality. His original mortality on the service, possibly 11% was soon reduced to 9%, to 7%, to 5%, with increasing experience and observance of surgical indications and solicitous after-care.

The attempt to introduce and popularize the operation of subtotal gastrectomy in this country fell in great part to Berg and to Lewisohn. The smugness and content with the operation of gastroenterostomy had first to be exposed and its fallacies publicized. The physiology of the newer operation was studied and demonstrated. The axiomatic declaration:—"no acid, no ulcer", was created to meet the facts, for the sacrifice of the antrum of the stomach and the survival of the acid-producing fundus still resulted in anacidity in the largest percentage of the cases. The opposition to the newer operation came from the rank and file of the surgical profession, high and low. "So big an operation for so little an ulcer" was an oft repeated and trite remark. The high incidence of gastro-jejunal ulcer was denied by many, the mortality of the new operation when practiced by green hands was emphasized. Those of us who so often attended medical meetings set to debate the subject can recall many a spirited heated session when Dr. Berg assuming the role of apostle presided and preached the merits of the gastrectomy to sceptical and obstinately set professional audiences. New York, Washington, D. C., Worcester, Mass., Montclair, New Jersey were memorable particularly for the vivid sparring of words and ideas and for the unconvinced looks on the faces of the strange members at the exposition of the philosophy and practice of the newer procedure.

Little by little the idea gained ground. Soon the operation was accepted for all gastric ulcers, slowly the procedure was agreed to by one group after the other for duodenal ulcers. The necessity to remove the duodenal cap with the ulcer *in situ* was hammered at, both by Berg and by Lewisohn; *ausschaltungs*, incomplete removals, insufficient sacrifice of antrum were denounced and demonstrated to be responsible for recurrent ulcerations. The decade of the nineteen twenties thus constituted for Mount Sinai and for Dr. Berg the successful prosecution of the campaign to popularize subtotal gastrectomy for peptic ulcer.

The encouragement and cooperation of Dr. Berg fostered the early work on regional ileitis. Faced with a puzzling and indeterminate clinical picture, one which had long been confused with and overclouded by the designation of

intestinal tuberculosis, he had the fortitude to operate upon and successfully to resect the first case of ileitis. Impressed by the pathological findings of a non-specific granulomatous lesion, good fortune rapidly brought to us two more identical cases for resection. The relationship of abdominal wall sinuses to this non-specific process led to combing of the follow-up material from the wards for identical cases. Soon, or between 1930 and 1932, fourteen such successful resections had been accumulated and studied, pathologically, histologically, bacteriologically and from the standpoint of etiology. When the question of publication was brought up Dr. Berg modestly declined co-authorship but pointed to the fact that two younger surgeons, Leon Ginzburg and Gordon D. Oppenheimer had under his encouragement been studying the pathology of non-specific granulomata and suggested the pooling of the clinical, surgical and pathological results of the two sets of studies. By every right Dr. Berg should have been one of the original authors of terminal, later, regional ileitis in 1932. Only his magnanimous consideration for younger men led him to withdraw his name and renounce his rights to a publication which opened a large field in the study of inflammatory lesions of the small intestine, a momentum which still carries far and still constitutes a field of study and interest twenty years and more later. The interest engendered in this study will always redound to the credit of the staff of Mount Sinai Hospital and helped to establish this institution as a center for study of intestinal diseases and their surgical treatment and cure. Another clinical picture which will always be associated with this institution and with Dr. Berg was the concept of right-sided or segmental ulcerative colitis. Not that regional colitis as a concept originated at Mount Sinai for the Mayo Clinic group and others had been conscious of the fact that not all colitis involved the rectum and sigmoid, and gave a positive sigmoidoscopic picture. But the life-history, the clinical features of this particular sub-species and particularly the surgical treatment and attack was worked out at Mount Sinai, Dr. Berg producing the earliest resected specimens and thus affording the opportunity for pathological study of this form of the disease. His operation of ileo-sigmoidostomy with isolation of the proximal sigmoid loop as a mucous fistula as a first stage operation followed in the course of weeks or months by resection of the diseased proximal colon was a brave undertaking in the days when antibiotics were unknown and when the slightest soiling of the peritoneal cavity meant post-operative infection, obstruction, peritonitis and a high and forbidding mortality. The publication of the first selective paper on segmental colitis in 1938 again opened a new field in the limited resection of the large bowel for localized forms of colitis.

The increasing utility of ileostomy for severe ulcerative colitis and the feasibility of subsequent total colectomy for otherwise incurable forms of universal colitis involving the whole colon and rectum as practiced early at Mount Sinai Hospital has all helped to establish the fact that this institution constitutes a center for the study of gastrointestinal diseases and a high-spot for the surgical treatment of such lesions.

To Dr. Berg and to his associates and successors belongs much of the credit

for such an achievement. In the earlier years Lewisohn was the Aaron who upheld the right hand of the prophet in the wilderness; by his incisive criticism, by his coldly scientific acumen, he maintained the middle-of-the-road and prevented enthusiasts from straying. Eventually with the passing of time, Dr. Berg approached the mature years that required him to relinquish the ward service. The ardors of the surgical service of gastroenterology were divided between Ralph Colp (1934) and John H. Garlock (1937), worthy successors of a tradition well established by Berg and Lewisohn in the previous decades, men well capable in their own right and by their own genius of carrying and of further advancing the interest in surgical gastroenterology which by now has been closely affiliated with the good name of the Mount Sinai Hospital.

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## SURGICAL ASPECTS OF PEPTIC ULCER

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In spite of the frequency of the occurrence of peptic ulcer, but in view of the uncertainty of its etiology, the surgical treatment of this condition has been applied so far without a sound rationale.

Though it is recognized that hyperacidity is not the cause of ulcer, there is enough to indicate that it is a potent contributory factor to the persistence and recurrence of an ulcer.

The rationale of surgical care is dependent upon the more or less accepted views on the physiology of the stomach and upper intestinal tract. An understanding of the process of acid secretion is fundamental for surgery to be effective. There are three phases in gastric secretion: one psychic, conducted by the vagus nerves; a second, the humoral phase is a chemical substance produced by the antrum of the stomach, and carried by way of the blood stream to the acid secreting glands in the fundus; and finally, there exists an intestinal hormone which causes a more or less continuous secretion in the stomach, the intestinal phase. The first two factors are of great importance in the surgical therapy of ulcer, the last one is, fortunately, of lesser moment. Over the first two, the surgeon has gained some control.

Partial gastrectomy was introduced into this country at about 1923 for the treatment of peptic ulcer, in the belief that if the chemical phase of gastric secretion could be eliminated or reduced, and an anacidity or hypoacidity created, conditions would be established for the cure of the ulcer. If this state continued, prevention of its recurrence could be expected. Accordingly, the antrum and pylorus of the stomach were removed, to exclude this second, or chemical phase of gastric secretion. This operation accomplished its purpose in a large measure. In the last 27 years it has come to be accepted by practically all modern surgeons as the operation of choice for this disease. However, this operation still had its drawbacks in that it was until recently, accompanied with a higher mortality than gastro-enterostomy. Furthermore there was still a certain recurrence rate, which, while much less than in gastroenterostomy, was still of considerable magnitude.

In recent years, Dragstedt with his experimental observations in mind has become the arch exponent of the division of both vagus nerves to the stomach. This operation is based on the concept that there is a large psychic element in the production of peptic ulcer. If the pathways carrying these psychic impulses from the brain to the stomach were interrupted, the acid secretion to the stomach would be greatly reduced. The patient would then be relieved of his symptoms and cured of his ulcer. These nerves were first cut in the chest cavity and later were approached infra-diaphragmatically. At first this operation was offered as

a definitive type of therapy, and later, because of some bad side-reactions it was combined with gastro-enterostomy.

Indeed, pain was relieved immediately in almost all patients, and it was also true that this operation could be accomplished with a very low mortality. However, the resultant morbidity, such as continuation of the ulcer as a silent disease, or at times perforating; gastric dilatation; and diarrhea were all factors which in many instances led to subsequent operations. These had to be done to relieve the foul belching of gas, the discomfort of a stomach which failed to empty, etc. Moreover, it has been shown by Moore that after about a year or more, the acid production returned to its initial level in many instances. Whether this is due to regeneration of the vagi or other causes is not known. If the latter observation is true, then the same condition, hyperacidity, prevails that provoked the original disease. If perchance a gastroenterostomy had been added as a complementary operation, there was now a state conducive to the formation of a marginal ulcer, a serious complication in the ulcer diathesis. Thus the past few years witnessed progressive waning of the enthusiasm for this type of operation. It has now only its originator and a few others as its adherents. Nonetheless, this operation is not to be discarded, as it has its indications and practical applications, as will be shown elsewhere in this paper.

In general, peptic ulcer is a medical disease, and becomes surgical in only about 10 per cent of the cases and only then when complications develop which cannot be successfully managed medically. Therefore, the surgical indications for the treatment of peptic ulcer are; perforation, pyloric stenosis, gastric ulcer, chronic duodenal ulcer with intractable pain, bleeding peptic ulcer, marginal ulcer.

Little need be said about the perforation of a peptic ulcer. When this catastrophe occurs, it is necessary to seal the leak, to prevent the occurrence of a peritonitis and a fatal outcome. It is well known, that for the most part, the mortality is directly proportional to the length of time that exists between perforation and operation. It is unfortunate that an overall mortality for this complication still ranges around 25 per cent because of delay in getting such patients operated upon promptly.

At this point, it may be said that the most innocuous procedure instituted by the surgeon serves best the patients' interest. This technique is usually a simple closure of the ulcer with perhaps the suture of a tab of omentum over the closure.

At different times surgeons have added a complementary gastroenterostomy, or performed a gastrectomy or, as has been recently advocated, added a vagotomy to closure of the ulcer. All these procedures invite additional risk, in a patient already being operated under adverse circumstances. Thus such procedures are not to be employed.

Recently there appeared recommendations for medical control of perforated peptic ulcer by the application of Wangensteen's continuous suction drainage, starvation and intravenous therapy. It would seem that in some cases this com-

plication was successfully managed in this way. It is conceivable that the small perforated gastric ulcer may lend itself to this therapy, but one cannot know beforehand how large the perforation is. Furthermore in perforation of a duodenal ulcer, where there is an associated pyloric spasm, it is readily understood how such a perforation could not be satisfactorily relieved by suction drainage. There are many other features in this type of treatment which preclude its use in general. Operation is the best therapeutic step to be employed, with emphasis upon early operation. It is not necessary to rely upon an X-ray for demonstration of free air under the diaphragm. Obliteration of liver dullness to percussion should not be a prerequisite. These signs will often be found wanting, and valuable time for attack will have been lost.

Pyloric stenosis is the next lesion which lends itself to successful surgery. In this lesion two conditions are to be considered. First, the stenosis caused by edema or spasm or both, due to an active ulcer, the second is stenosis due to an ulcer which has gone on to healing and has reached the stage of fibrosis and cicatrization.

The former must be carefully differentiated from the latter. One often sees in the former category, patients, who are frequently in the older age groups with histories of long standing. An exacerbation of pain and persistent vomiting indicate a stage of stenosis which is due to edema of the pylorus. X-ray studies may show a 24 hour retention of barium in the stomach. These patients should be treated by gastric lavage and continuous gastric suction drainage by means of a Wangensteen apparatus.

Concurrently the patient should receive plasma and blood to correct the hypo-proteinemic state which has resulted from starvation and vomiting. Electrolytes, especially sodium chloride must be supplied along with glucose, water and vitamins. By such management many cases of pyloric obstruction will be relieved and then the patient placed under a good medical regime, may be re-evaluated for need of surgery when the general and local condition have improved.

If organic pyloric stenosis exists as a result of scarring, in a healed duodenal ulcer, then surgery is imperative. Here is a fairly rare situation, in which it is probable that the ulcer diathesis has spent itself and an active ulcer is no longer present, and the final result is a scarred pylorus,—a gastro-enterostomy may be performed to provide for drainage of the stomach. This operation, under these circumstances, is particularly useful because this situation often occurs in elderly patients, and this relatively simple procedure, exposes the patient to a lesser risk than if the radical operation were employed.

The consideration of gastric ulcer as a medical or surgical problem differs from the concept employed in a deliberation on duodenal ulcer. Here malignancy is a serious question. There are no definite criteria for determining whether a gastric ulcer is benign or malignant. Only the histologist, and not always can even he make this differentiation. Malignant transformation of a benign ulcer though probably rare, is said to occur. Several criteria have been offered for a

differential diagnosis, and it has been said that if an ulcer is larger than a twenty-five cent piece, it is malignant. But defects of a lesser size have been found to be malignant while lesions the size of the palm of a hand have occasionally proved to be benign.

The location of the ulcer has some significance. If found upon the greater curvature, the likelihood of its being a carcinoma is very great. At the re-entrant angle, the chances for benignity are good. Prepyloric ulceration is often benign. Juxta cardiacae and posterior wall ulcers are usually malignant, but may be benign.

X-ray studies aid substantially in the interpretation of a gastric lesion, and the criteria employed by the roentgenologist provide a high degree of accuracy. Nevertheless, a report of benign ulcer is always fraught with the possibility that the lesion may be malignant. The radiologist is very useful in a comparative interpretation of repeated gastric series. He is best prepared to study changes in the stomach wall before and after treatment. However, niches which were believed to have been due to benign ulcer have subsequently been shown to have resulted from carcinoma which had gone on to some healing. There occurs during treatment sloughing of necrotic tissue, relieving edema in the area with formation of granulation tissue. This may even result in partial or complete epithelialization, the latter to last only for a brief period, when the underlying disease again becomes apparent.

Acid secretion studies are not of great service. Normal acidity or even hypo-acidity may be found in a benign gastric ulcer. It is not uncommon to find normal acidity in the presence of a carcinomatous lesion. At present, the Papanicolaou studies of gastric washings have not been very successful; a negative result being without significance, a positive result is rarely obtained, because of the rapidity of the disintegration of the exfoliated cells, while false positives are misleading.

Some progress has been attained in electro-potential studies of the stomach. However, this method at present is used in a very limited way and is not as yet practical.

Gastroscopic observations can be of definite assistance, but also have many shortcomings. Not alone, can one err in the interpretation of the observed lesion, but there are at times encountered blind spot areas in the stomach which cannot be visualized. Some assistance is rendered by this method in follow up studies but not with a definitiveness and assurance of infallibility.

From the foregoing it may be concluded that the radiologist, internist, gastroscopist and biochemist cannot offer positive proof that a lesion is benign or malignant. The surgeon, with the lesion in his hand at the operating table is also often at a loss to interpret his findings. The pathologist with the gross specimen before him must often hedge and await his microscopic studies, only to be chagrined at times by false interpretation.

Under these circumstances what should the therapy for gastric ulcer be? If the lesion carries with it the possibility of malignancy or a small chance for malignant change, then it would seem logical to do a partial gastrectomy.



Situations may arise in relatively young individuals with a short history, in which medical therapy may be advisable. This should be carried out for 4-8 weeks and the patient restudied. If the X-ray has become negative, gastroscopy is negative, and occult blood absent from the stools, then medical observation should be continued. However, it would appear to be safer to treat gastric ulcer the same way as other suspicious malignant conditions elsewhere in the body are treated, by removal.

While duodenal ulcer is a medical disease and comes within the province of the internist, it is not without surgical indications when accompanied by intractable pain. When such an ulcer burrows into the head of the pancreas or penetrates adjacent viscera, the reaction set up is sometimes irreversible, and medical management fails to give relief of symptoms. The patient is obliged to visit, and revisit the hospital; he becomes incapable of holding his job and no longer able to provide for his family. The physical handicap becomes enhanced by a disturbed psyche.

When intractability of pain is considered we do not mean the type of patient who refuses to follow medical advice and therefore continues to suffer the ravages of his disease. Such a person is not entitled to serious consideration by the surgeon. The latter approaches his task with the understanding that he is to succeed where his medical colleague has failed. It may be assumed that if the patient has not been cooperative with his physician, he probably will do no better with his surgeon. Because the surgeon retires soon after the operation, the internist is again presented with the problem of the recalcitrant patient. The results in such cases are far from satisfactory.

In the case of a chronic duodenal ulcer, the operation should be a partial gastrectomy, and whenever possible the ulcer should be removed. In patients who pre-operatively show evidence of a high degree of acidity and those who have a marked nervous component, a bilateral vagus nerve section may be added. This may prevent the formation of a marginal ulcer. The addition of the section of the vagus nerves is not accepted by all as necessary or even as desirable, but in the case just mentioned there may be good reasons for its performance.

A serious problem is the treatment of the patient with massive gastro-duodenal hemorrhage. It is essential, of course, to eliminate other causes of hemorrhage from the gastro-intestinal tract, such as varices of the oesophagus due to cirrhosis of the liver, portal hypertension, tumors of the small and large bowel, Meckels' diverticulum etc. To establish the presence of a gastro-duodenal ulceration, it may be necessary to do a gastro-intestinal series on a patient who is bleeding, using a thin barium mixture, and avoiding as much manipulation as possible by the roentgenologist. It is a great advantage to the surgeon to know first, that there is an ulcer present and secondly, to know its location.

Before advancing with this problem it is well to define the meaning of massive hemorrhage as lack of a definition has led to a great deal of confusion. It may be said that a patient who enters the hospital in shock with a hemoglobin of less than 7 Gm. and a red blood count of less than 2,500,000, who needs 2500 cc or

more of blood to restore his volume to normal, has met the diagnostic requirements of massive hemorrhage.

The responsibility for the care of such a patient is very great. The patient should be admitted directly to the surgical service, the medical man invited to consult regularly and the surgeon choosing the opportune time, if operation is to be done. If this is not acceptable the reverse should be done and the surgeon see the patient on the medical service every hour. However, both physicians must collaborate closely to obtain the optimum result. The pulse and blood pressure must be taken and recorded every one half to one hour day and night; hemoglobin and hematocrit studies should be done regularly. If facilities are present for blood volume studies they should be carried out. Plentiful supplies of blood must be at hand and given, and its effects on the patient noted. Gastric suction should be continuous. Whether feeding is to be done or not, is a moot question. Recently buffer solutions have been advocated for intragastric therapy but their effectiveness is not entirely certain.

The question that arises is where shall conservative therapy cease and radical surgery begin. If surgical intervention is decided upon nothing less than a partial gastrectomy with excision of the ulcer is the procedure of choice. Ligation of bleeding vessels in the ulcer, ligation of the gastro-duodenal artery, and other palliative procedures are without merit and hemorrhage often will continue after the abdomen is closed.

Fortunately, this kind of case is relatively infrequent, but when it does occur, it should be evaluated in the following manner. If the patient is under 50 years of age the chances of the bleeding stopping are relatively good. If above this age, the prognosis is bad. If the ulcer is located in the stomach the outlook is worse than if located in the duodenum, because larger vessels are usually eroded in the stomach. If the patient has had a massive hemorrhage, a decision must be arrived at in the first 48 hours for patients below 50, and preferably in the first 24 hours if the patient is over 50, with the period calculated from the time the bleeding began. If the patient has been bleeding for longer than 48 hours, the prognosis following surgery is very poor. The surgeon has a right not to invite the chances of an inevitable mortality. In this time anoxia and anemia of the tissues has occurred. Even if the patient recovers from the immediate operation he is a candidate for complications due to hypotension with its concurrent cardiac complications, and failure of proper healing of suture lines with duodenal "blow-out," infection, and peritonitis.

If the patient has stopped bleeding after his first brisk hemorrhage, he may be carefully observed and prepared for interval surgery within four to six weeks after the initial hemorrhage. This in all likelihood will preclude another hemorrhage at some future time. The large group of patients below 50 years will fall into this category.

For the patient who has stopped bleeding and then has a recurrence while he is being observed, which will usually happen in the first three days after the initial hemorrhage, no time should be lost in again treating this patient conser-

vatively. With plenty of blood on hand, he should be immediately operated upon.

Just a few words before concluding, on another complication of ulcer, namely jejunal or marginal ulcer. This may follow resection or gastro-enterostomy. In many instances, this man-made situation, responds to medical therapy, but in other instances, the ulcer is subject to all the complications which have been considered, with the exception of malignant transformation.

If surgery is indicated, and a previous adequate partial gastrectomy has been done, it is sometimes advisable to do a bilateral supra- or infra-diaphragmatic vagotomy. The latter approach has the advantage of giving the surgeon a chance to inspect the lesion. If gastroenterostomy alone has previously been done, one may still do the section of the vagus nerves, but preferably a partial gastrectomy should be done, with or without nerve division.

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# CHANGES IN GASTRIC ACIDITY AND MOTILITY IN A CASE OF BILATERAL SUBPHRENIC VAGOTOMY ALONE FOR DUODENAL ULCER

(11 Year Follow-up—Immediate and Late Effects)

ALBERT CORNELL, M.D.

Previous vagotomies which have been performed below the diaphragm were incomplete since they were unilateral or did not consist of a resection of the nerve. Many were performed for functional conditions such as gastric ptosis or tabetic crisis or were combined with some other procedure such as gastroenterostomy (1). Pieri reported bilateral resection of the vagus nerve in 14 cases of gastric spasm, recurrent ulcer after gastric resection or gastroenterostomy, and in gastric juxta-cardiac ulcer but none in duodenal ulcer (2).

The case to be described is presented because it is probably the first known case of attempted "complete" subphrenic vagotomy for duodenal ulcer performed without any other operation. In 1941, Colp (3) reported two cases of vagotomy, one of which was performed in November 1939 for a large gastrojejunal ulcer which had developed following subtotal gastrectomy with prepyloric exclusion for duodenal ulcer. In this case a transthoracic supradiaphragmatic bilateral vagotomy was performed. The second case was one of infradiaphragmatic anterior vagotomy, done in October 1940 for a large gastrojejunal ulcer, also following a previous subtotal gastrectomy for bleeding duodenal ulcer. In addition to the vagotomy, a Stierlin procedure on the cardia and a jejunostomy were performed. Insulin tests carried out in both these cases, preoperatively and post-operatively showed no essential differences. In 1944, Weinstein, Colp, Hollander and Jemerin (4) reported additional cases of vagotomy performed above and below the diaphragm and discussed their results. In June, 1943, Dragstedt (5) presented his experiences with the transthoracic approach for vagotomy as a cure for gastroduodenal ulcer. Thus, our case is of historical interest, having antedated Dragstedt (who later turned to the subphrenic route), by about four years, since this patient was operated upon on April 22, 1939.

This patient was observed for over 11 years following the operation and had undergone many studies (clinical, x-ray, and test meal) showing the immediate and late effects of such a procedure without gastroenterostomy having been added. This is probably one of the first cases to be studied with the insulin test. It was possible to note the effects of vagotomy on other organs, thus providing very useful information, since vagotomy has been advocated for ulcerative colitis, ileitis and other conditions.

## CASE REPORT

*History.* R.S., a woman aged 40 years, entered The Gastrointestinal Clinic of The Mount Sinai Hospital Out-Patient Department in October 1936. She complained of epigastric pain, two to three hours after meals and during the night. Her weight was 148 pounds. For the previous seven years, she had had this pain accompanied by nausea and vomiting.



A gastrointestinal x-ray series in October 1936 (fig. 1) had revealed a marked deformity of the duodenal bulb. In July 1937, she was admitted to the hospital. For the previous 2 weeks she had had epigastric pain accompanied by vomiting and followed by some hematemesis and the passage of one tarry stool. At this time, radiographs again revealed a deformity of the duodenal bulb. Her free acid was  $84^{\circ}$ , total acid,  $98^{\circ}$ . She left the hospital to re-enter in November of 1937, complaining of epigastric pain and burning. X-ray studies of the gastrointestinal tract revealed again a duodenal deformity with a normal gall bladder series. Subsequently she was admitted to the Coney Island Hospital because of vomiting and tarry stools; she required blood transfusions. Here, too, x-ray studies of the gastrointestinal tract were positive for duodenal ulcer. She gained weight to  $155\frac{1}{2}$  pounds in December 1938.



FIG. 1. Preoperative radiograph showing typical duodenal ulcer (October 26, 1936).

She also had an admission to the Morrisania Hospital for recurrent hematemesis and tarry stools of three weeks' duration, but was not transfused. Here also gastrointestinal x-ray studies revealed a duodenal ulcer. She re-entered The Mount Sinai Hospital in April 1939 because of pain, nausea and regurgitation of watery material. Except for some deep epigastric tenderness, her physical examination was negative. A "vagus (orange-chewing) test meal" revealed a free acid of  $78^{\circ}$  and a total acid of  $88^{\circ}$ .

*Course.* In view of the history of hematemesis and melena, persistent symptoms and positive x-ray findings, the patient was operated upon by Dr. Percy Klingenstein (Service of Dr. Ralph Colp) on April 22, 1939. The stomach and duodenum by appearance and palpation were found to be normal. The gall bladder was slightly thickened but no stones were palpable. Because of these findings, it was not deemed advisable to operate on the stomach, but in view of the hyperacidity, it was decided to attempt a vagus section. The esophagus was exposed at the esophageal opening into the diaphragm and nerve branches divided on



FIG. 2. Postoperative radiographs showing mottled appearance of the gastric mucosa due to retained food and mucus.



FIG. 3. Postoperative radiograph showing gastric retention of barium at 6 hours (October, 1939).

both anterior and posterior aspects. The excised filaments were studied microscopically and reported as "fragments of nerve tissue without significant change". The negative exploratory findings in the presence of a deformed duodenal bulb, hyperchlorhydria, and repeated episodes of gross hemorrhage are not unusual, as they have been reported by other observers.

Following the operation, the patient complained of foul breath, nausea and regurgitation of food, probably due to marked delay in gastric emptying. The stomach became dilated and gastric lavages revealed marked food residues with foul odor. Many test meals revealed free acidities ranging from  $50^{\circ}$  to  $100^{\circ}$  and food retained from the night before.



FIG. 4. Postoperative radiograph showing slow progression of the barium to splenic flexure of the colon at 24 hours (October, 1939).

A postoperative orange-chewing "vagus test" meal, even though done only 10 days post-operatively, showed a free acid of  $40^{\circ}$  and a total acid of  $82^{\circ}$ . A gastrointestinal x-ray series in June 1939 showed the stomach to have a mottled appearance due to food or to a marked mucus deposit on the mucosa although the patient stated that she had not eaten in the previous 14 hours. The bulb was complete but there was a gastric residue at 6 hours of 25%. The small bowel was studied at intervals and showed no definite abnormality in pattern or motility. The barium was in the cecum at 4 hours. Her weight dropped to 144 pounds in August 1939. These symptoms continued until October 1939 when she re-entered The Mount Sinai Hospital because of complaints of regurgitation of food and foul breath. At this time she appeared to have considerable retention of foul gastric contents. A gastrointestinal series, however, revealed a peculiar mottled character to the mucosal pattern of the stomach (fig. 2). The duodenal bulb was difficult to visualize but seemed to show no definite ab-

normality. There was stasis of the second and third portions of the duodenum without obstruction; at 6 hours, there was still a marked residue in the stomach (fig. 3); at 9 hours, there was still a 25 per cent residue in the stomach, which had emptied completely at 24 hours, but the colon was incompletely filled (fig. 4). A fasting blood sugar test taken at this time was 90 mg. per cent.

In February 1940, because of epigastric fullness and vomiting she was again studied on the wards of The Mount Sinai Hospital. Gastric aspiration 12 hours after ingestion of prunes revealed many retained shreds. A gastrointestinal x-ray series showed retention of solid food and there was a slight deformity of the bulb insufficient to diagnose a duodenal ulcer. There was a 25 per cent residue of barium at 6 hours. Gastroscopy showed "practically no well-formed rugae. The mucosa was markedly dry with food particles and crust-like secretion clinging to it. The pylorus was well visualized and appeared to have normal contractility". The free acid by Rehfuess test meal was 46° and by insulin test was 44°. By October 1940, the patient had improved on 3 lavages per week but by May 1941, her weight



FIG. 5. Postoperative radiographs showing normal duodenal bulb (March, 1941)

had dropped further to 133 pounds, a loss of 22½ pounds for the 2 years of the postoperative period. At this time tests for the presence of pepsin were positive in fasting specimens. In addition, after insulin hypoglycemia there was a rise in free acidity thus indicating an "incomplete vagotomy".

A gastrointestinal x-ray series in March 1941 disclosed a hazy reticulated gastric mucosa as previously described. There was no duodenal lesion (fig. 5) and the motility of the small bowel and stomach was normal. In September 1941, the patient continued to complain of persistent epigastric fullness and occasional vomiting. In March 1942, there was overnight retention of food and an insulin test revealed a rise in free acidity up to 80° and a total acid of 115° indicating an incomplete vagotomy. Her weight continued to remain at 133 pounds. A gastroscopy repeated in November 1942 was negative except for sluggish peristalsis.

A gastrointestinal x-ray series in September 1945 showed no deformity of the esophagus, stomach or duodenum. The peristaltic activity in the stomach was irregular; the waves



did not pass continuously and completely through the stomach. The mucosal pattern was normal. Gastric emptying proceeded at a normal rate: at 2 hours most of the barium was in the jejunum and proximal ileum, at 6 hours, the stomach was empty—the barium was mostly in the ileum and cecum. However, a motility test still showed many prune and raisin skins retained overnight although only 20 cc. of fasting contents could be aspirated.

In May 1946, an Ewald test meal revealed 5 cc. of retained, undigested food with a free acid of 12° and a total acid of 44°. In March 1947, a gastrointestinal x-ray series showed no abnormality in the esophagus, stomach and duodenum. In June 1948, she still had nausea one half hour after meals but her weight at this time was 145 pounds. Although she had no epigastric pain, she still had one or two attacks weekly of vomiting of much mucus and undigested food. Her appetite was good despite a recent nervous upset (her daughter had just been operated upon for a brain tumor). In October 1948, an insulin test was done with a moderate response, with the free acidity up to 58° and total acidity of 66°. An overnight motility test meal done with prunes showed no evidence of retention with only 18 cc. of fluid present. There was some mucus with no free acid and a total acid value of 10°. She still had occasional nausea and felt bloated after meals. She also complained of anorexia, occasional diarrhea and foul belching at times. She tired easily, felt faint and perspired whenever she had epigastric discomfort. Despite these symptoms, which may also have been aggravated by the menopause, her weight remained stationary at 144 pounds.

In December 1948, the following laboratory studies were made:

*Galactose tolerance test.*

	Blood sugar	Urine
Fasting	94 mgm. %	0
After ½ hour	125 mgm. %	0
After 1 hour	137 mgm. %	0
After 2 hours	83 mgm. %	0
After 3 hours	62 mgm. %	0

*Cephalin flocculation test.* 3+

*Gastrointestinal X-ray series.* No abnormality of the esophagus or stomach. Tonus and peristalsis were practically normal. The duodenal bulb was complete. The small bowel studied frequently showed no evidence of abnormality in pattern or motility. Three hours later, there was no gastric residue and the head of the barium column had reached the cecum. At 6 hours, the barium extended from the terminal ileum to the splenic flexure of the colon. At 24 hours there was no evidence of progression in the colon and only very slight progression at 48 hours.

More recent studies, made in November 1949, disclosed the following:

*Cephalin flocculation test.* 4+

*Fasting blood sugar.* 90 mg. per cent.

*Thymol turbidity test.* 2.6 units

*Stool examination.* No evidence of excess fat or starch and no ova or parasites.

*Blood count.* Hemoglobin 12.8 Gm.

White blood cells	5,400
Segmented	39 per cent
Lymphocytes	51 per cent
Monocytes	10 per cent

*Glucose tolerance test.*

	Blood sugar	Urine
Fasting	110 mg. per cent	0
After ½ hour	200 mg. per cent	0
After 1 hour	120 mg. per cent	0
After 2 hours	99 mg. per cent	0
After 3 hours	70 mg. per cent	0

*Weight.* This had risen to 149½ pounds (fig. 6).

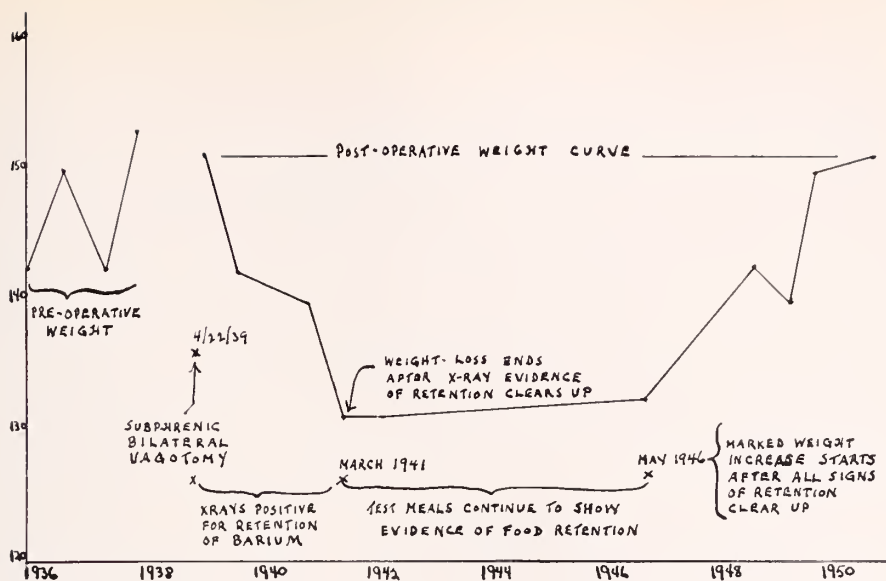


FIG. 6. Progress chart of patient before and after subphrenic vagotomy.

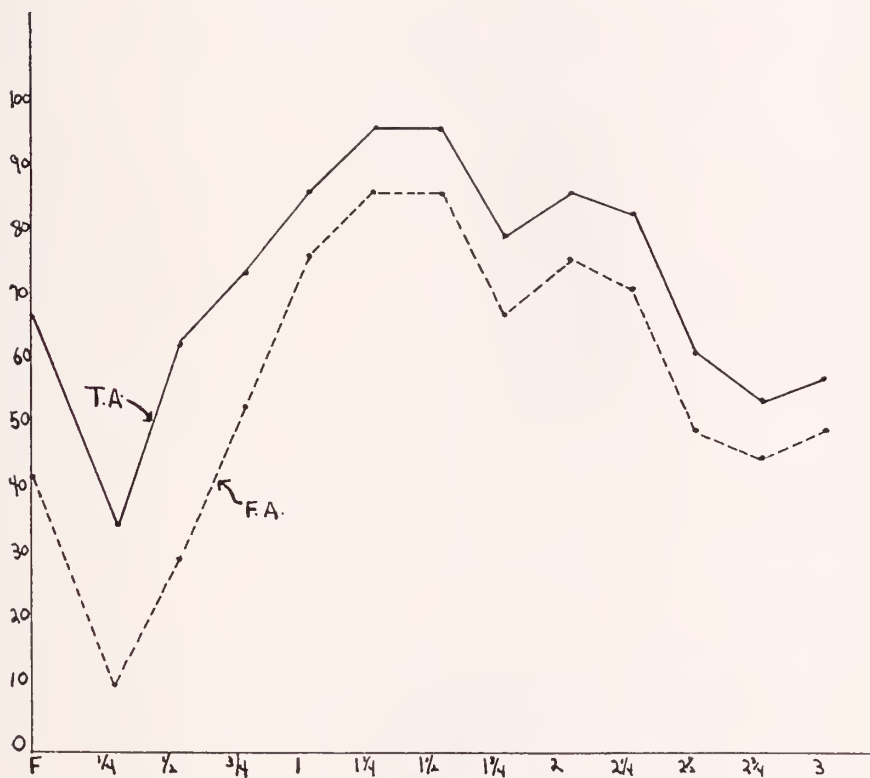


FIG. 7. Preoperative gruel test meal (July 20, 1937).

F—Fasting contents

F.A.—Free acid

T.A.—Total acid

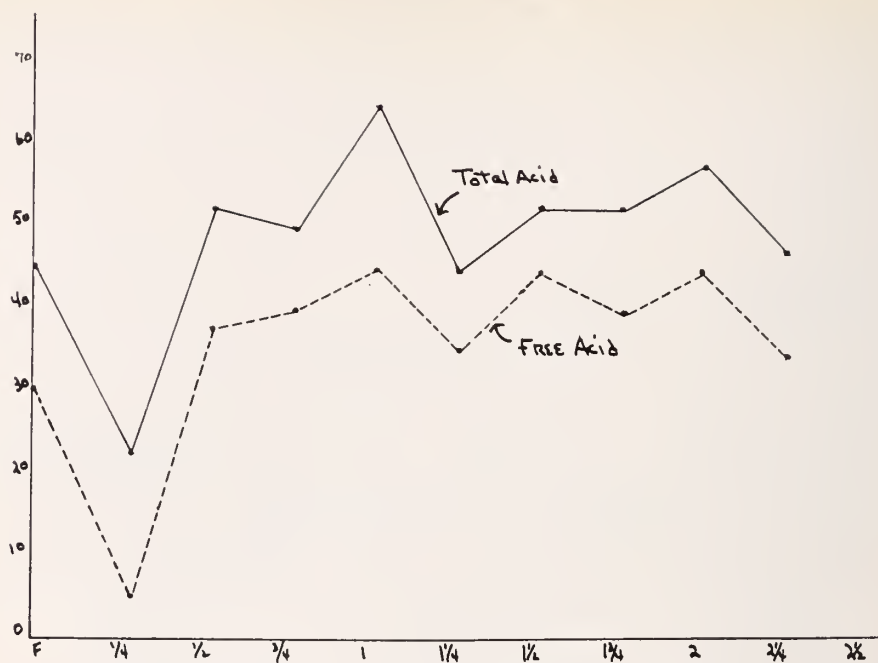


FIG. 8. Preoperative gruel test meal (October 14, 1937).  
F—Fasting contents

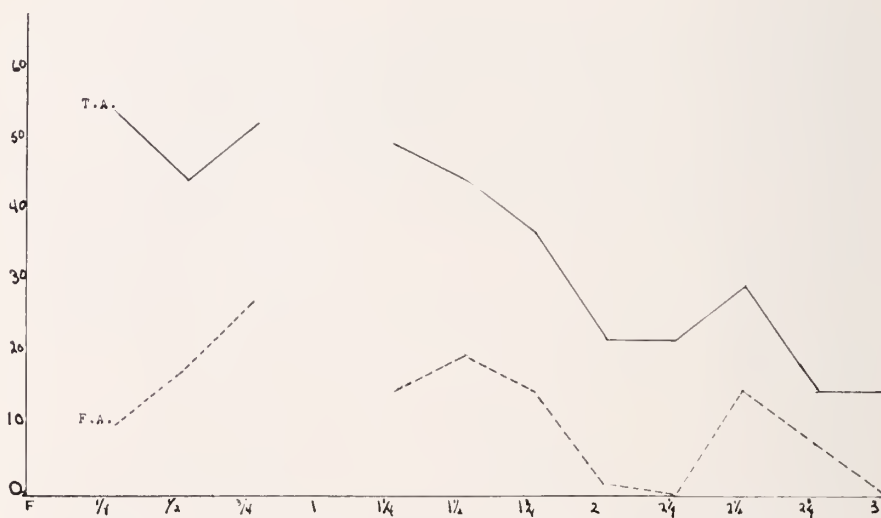


FIG. 9. Gruel test meal 6 months postoperative (October 25, 1939).  
F—Fasting contents  
F.A.—Free acid  
T.A.—Total acid

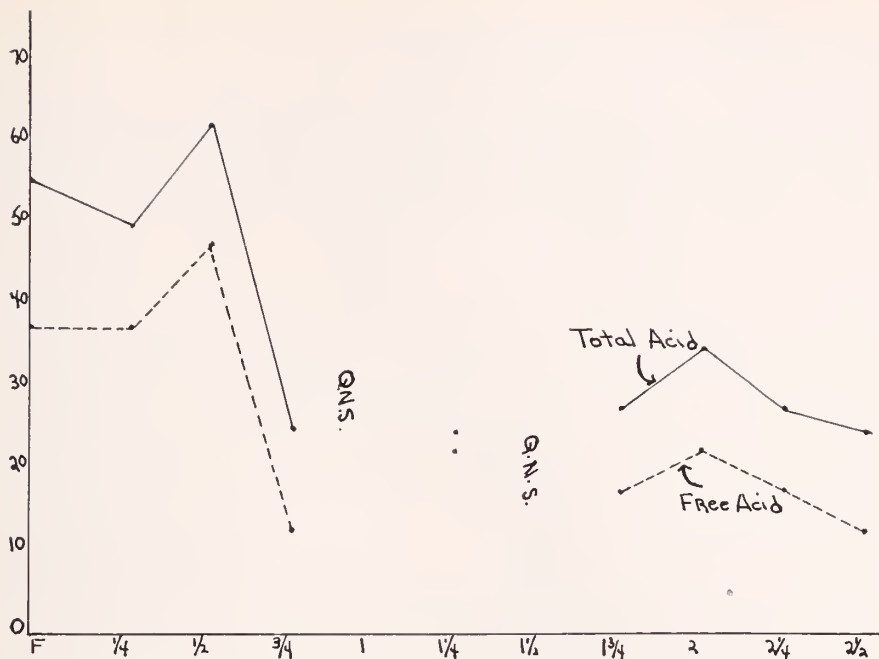


FIG. 10. Gruel test meal 10 months postoperative (February 26, 1940).  
F—Fasting contents

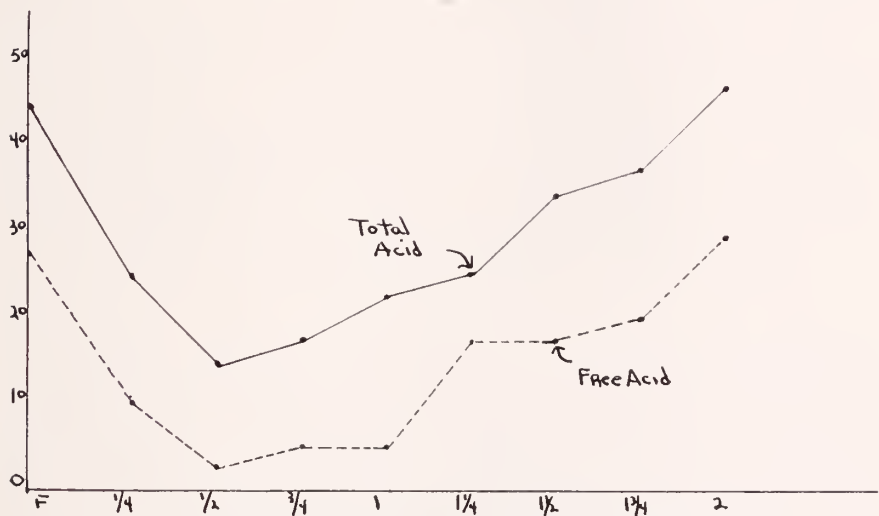


FIG. 11. Gruel test meal 2 years postoperative (April 7, 1941).  
F—Fasting contents



## DISCUSSION

The foregoing observations indicate that:

1. Since the insulin test was still positive after many years, the vagotomy was incomplete.
2. The motility disturbances were quite severe for 2 years and persisted to some degree of severity thereafter. But, despite these symptoms, gastroenterostomy was not required. According to Machella (6) and others, retention following

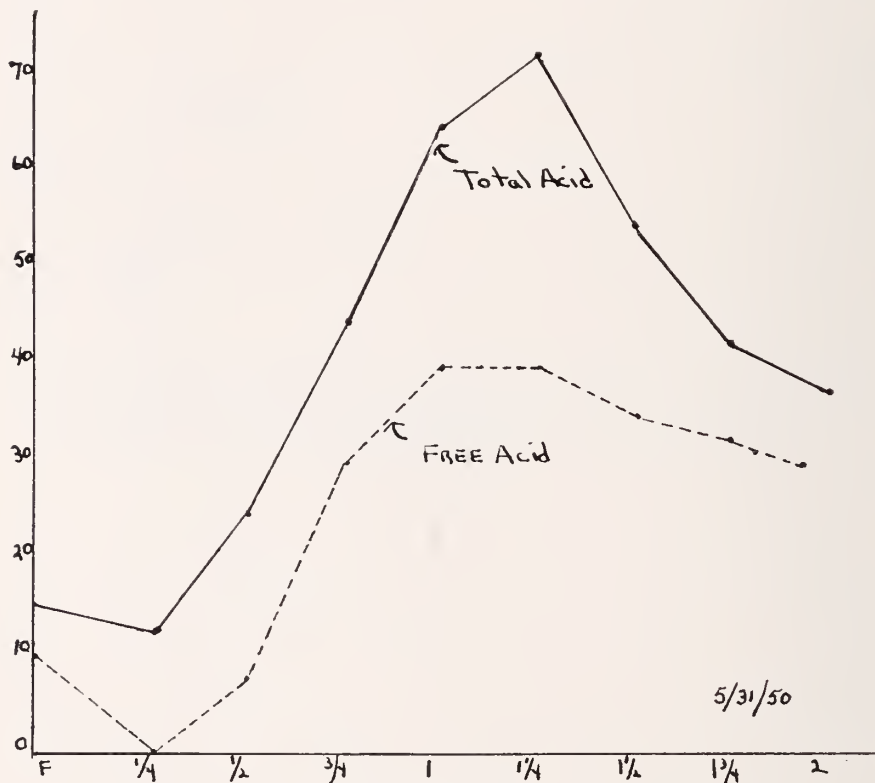


FIG. 12. Gruel test meal 11 years postoperative (May 31, 1950).  
F—Fasting contents

vagotomy usually lasts 2 to 13 months, and many patients require a second operation for relief. Urecholine (Merck) was not available at that time.

3. The ulcer symptoms disappeared without further hemorrhage and many radiographic studies showed a normal duodenum. Thus, the vagotomy, although incomplete, apparently healed the ulcer. Boekus (8) stated recently that "vagotomy exerts a beneficial healing effect on many individual ulcers."

4. The test meals showed a lowered acidity several years after the vagotomy in response to gruel (figs. 7 to 12) and alcohol (figs. 13 to 16).

According to the recent work of Schoen (7) bilateral vagotomy without gastro-

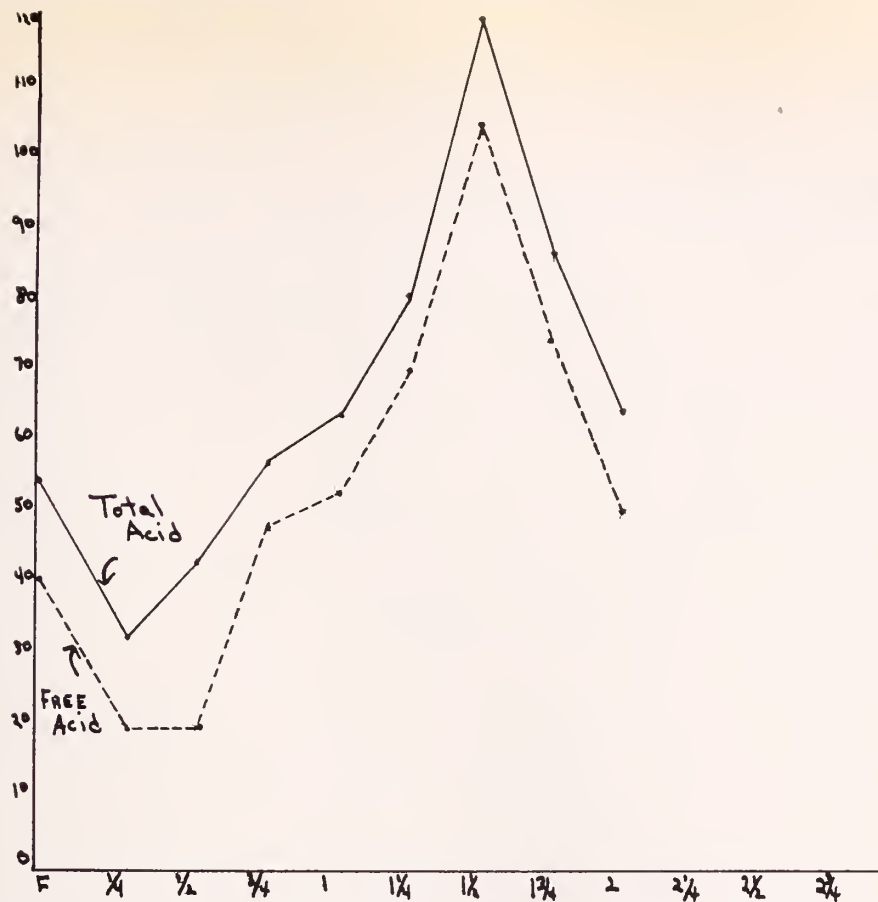


FIG. 13. Preoperative alcohol test meal (November 18, 1938). F—Fasting contents

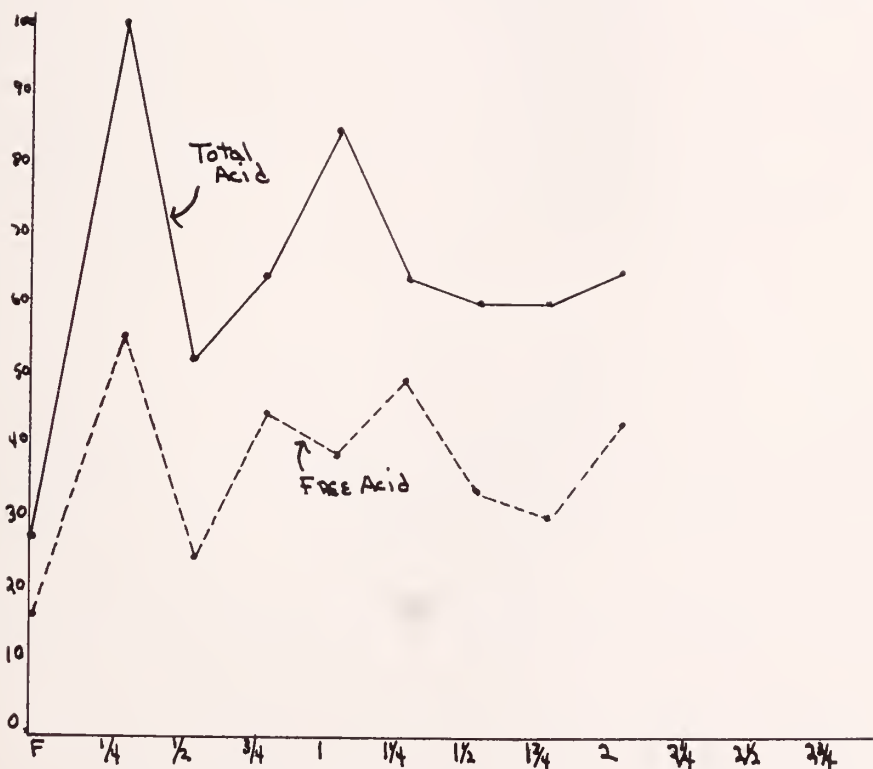


FIG. 14. Alcohol test meal 3 months postoperative (July 24, 1939). Marked retention of food in all specimens. F—Fasting contents

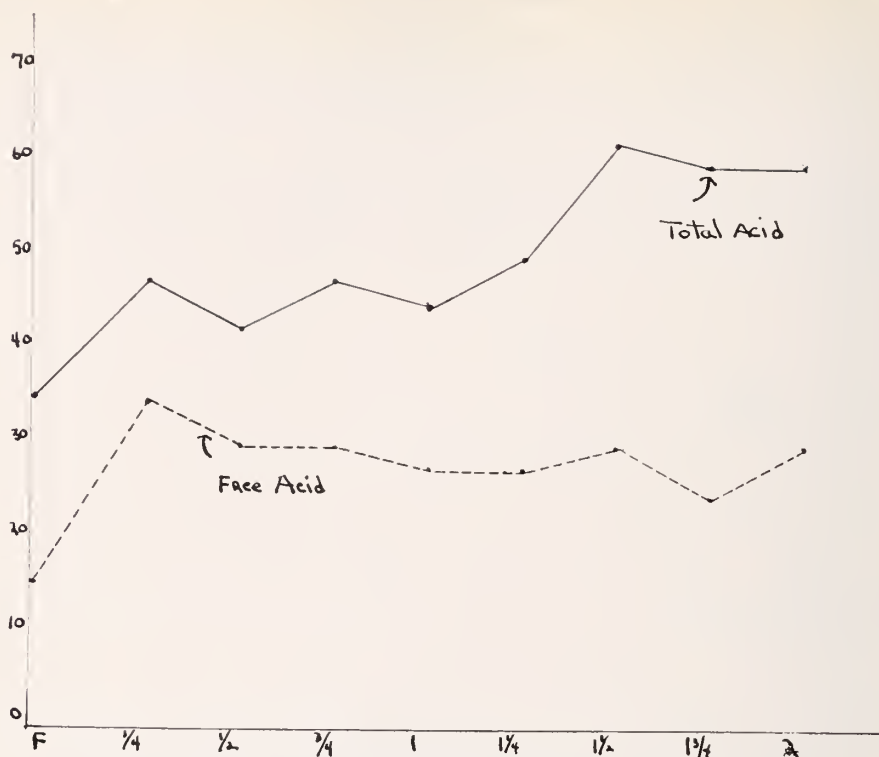


FIG. 15. Alcohol test meal 16 months postoperative (August 12, 1940).  
F—Fasting contents

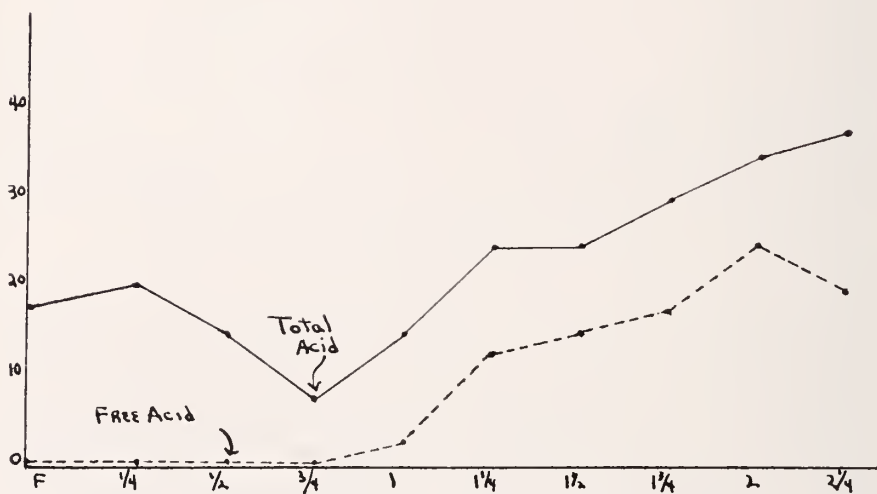


FIG. 16. Alcohol test meal 1 1/2 years postoperative (October 14, 1940). Retained food in all specimens.

F—Fasting contents

enterostomy produces a decrease in the rate of gastric secretion by decreasing or abolishing the cephalic phase. The humoral phases are also reduced as shown

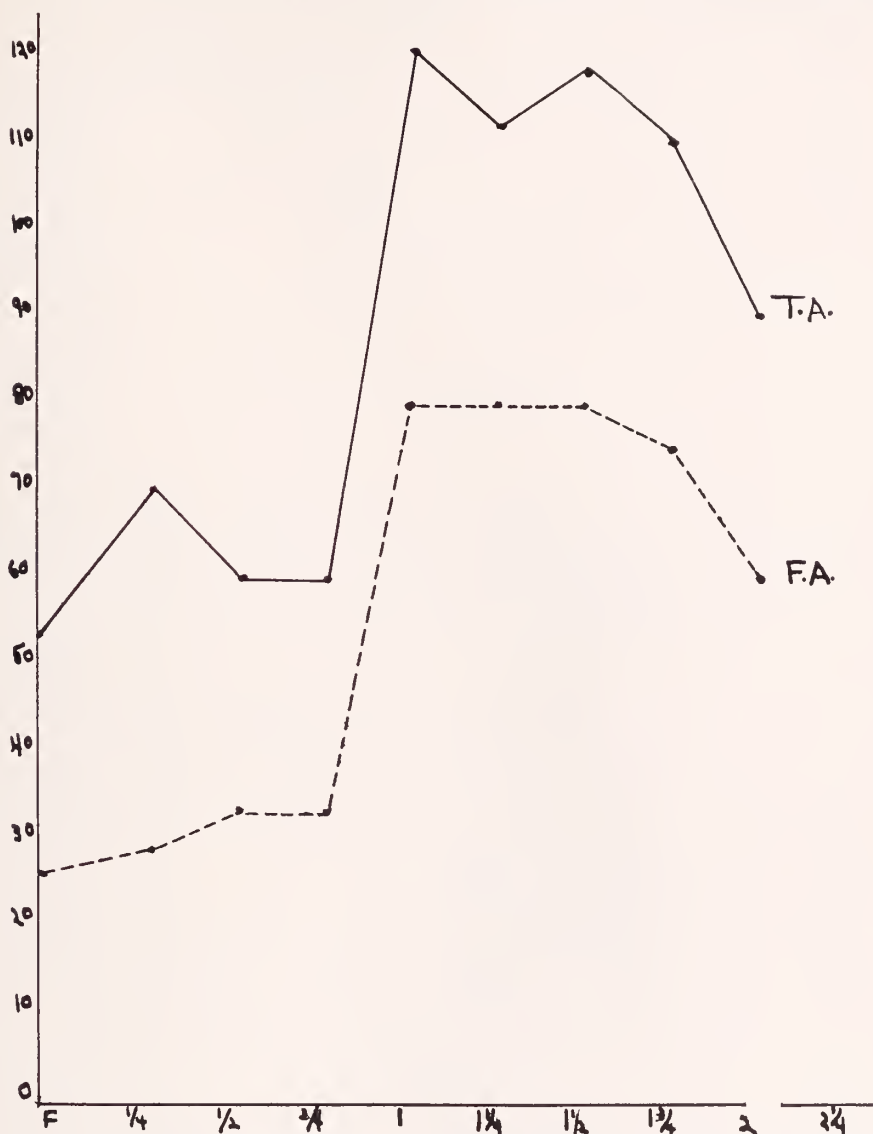


FIG. 17. Insulin test 3 years postoperative (March 18, 1942). Fifteen units of insulin intravenously. Retention in all specimens of undigested food. Fasting blood sugar, 70 mg. per cent. Blood sugar, 30 mg. per cent 55 minutes after insulin.

F—Fasting contents

F.A.—Free acid

T.A.—Total acid

by the response to an Ewald meal or histamine. He also notes that vagotomy, unlike subtotal gastrectomy, permits gastric juice to empty directly into the



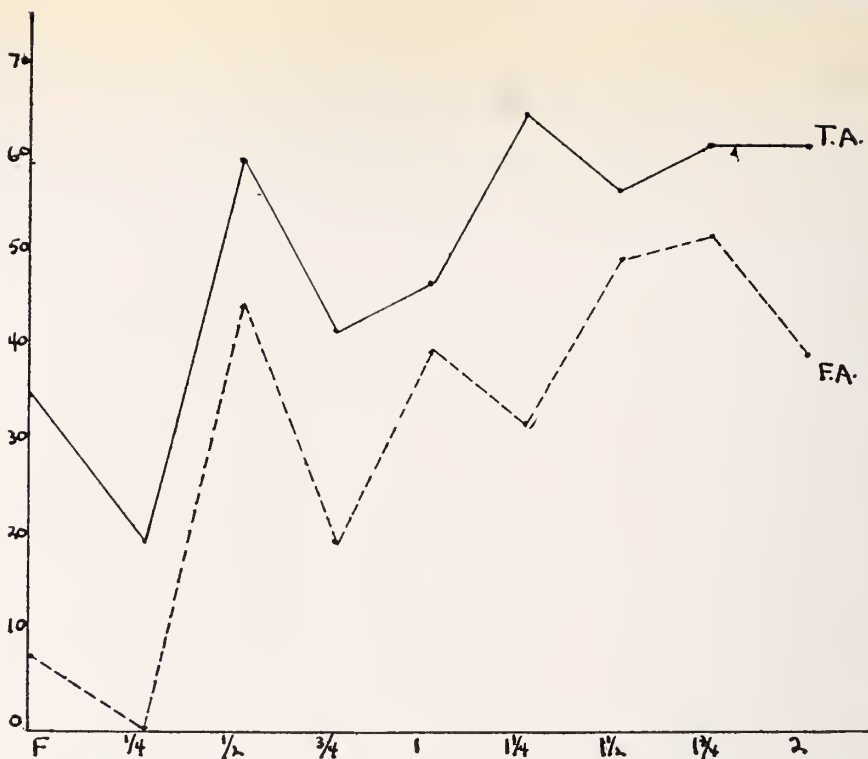


FIG. 18. Insulin 7 years postoperative (May 10, 1946). Fifteen units of insulin intravenously. Blood sugar 1 hour later, 15 mg. per cent.

F—Fasting contents F.A.—Free acid T.A.—Total acid

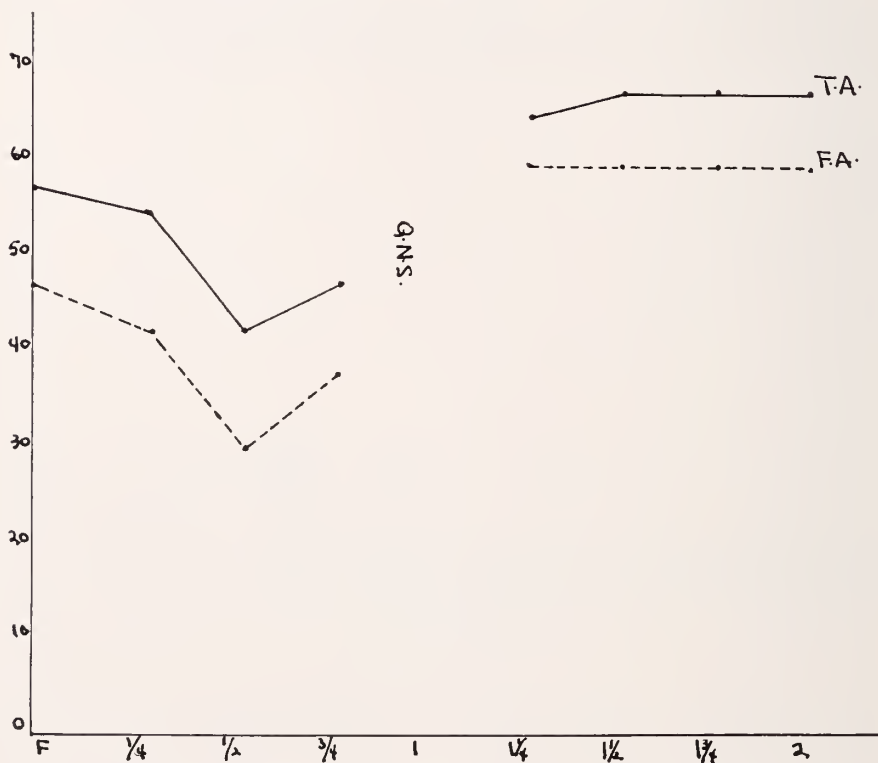


FIG. 19. Insulin test 9 1/2 years postoperative (October 11, 1948). Fifteen units of insulin intravenously. Fasting blood sugar, 90 mg. per cent. Blood sugar 1 hour after insulin, 15 mg. per cent. F—Fasting contents F.A.—Free acid T.A.—Total acid

duodenum and therefore those duodeno-gastric mechanisms which may operate to suppress gastric secretion and motility are not necessarily abolished as they are after subtotal gastrectomy. According to Schoen's studies, vagotomy decreases the acidity 83 per cent, the peptic power 57 per cent, rate of secretion of free acid by 91 per cent and the secretion of peptic units per minute by 73 per cent from the preoperative rate.

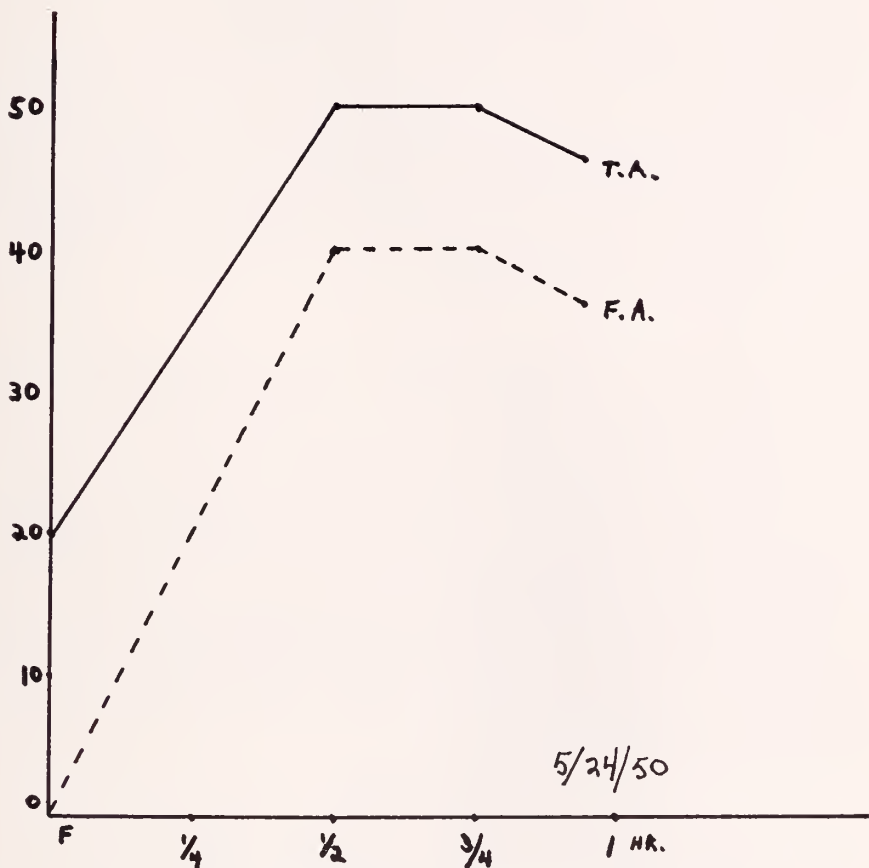


FIG. 20. Histamine test meal 11 years postoperative (May 24, 1950).

F—Fasting contents

F.A.—Free acid

T.A.—Total acid

Moreover, Moore, who has one of the best studied groups of vagotomy, according to Boekus (8), reports a resumption of the preoperative gastric secretory pattern in from 2 to 4 years in some of his cases. Others have had similar experiences. According to Weinstein *et al.* (4), the persistence of the acid response to insulin as illustrated in our case (figs. 17 to 19) proves that little reduction in the nervous phase of secretion can be expected from partial vagotomy.

5. The subjective symptoms as a result of the motility disturbance cleared up

eventually although there were minor signs of motor trouble long after the severe gastric retention had been relieved. The patient has also been able to regain much of her weight.

6. Gastrointestinal x-ray studies now reveal no disturbances of function in the esophagus, stomach and small bowel. There appears to be good passage of the barium meal to the splenic flexure at 6 hours. However, beyond this there is only slow progression through the colon, even at 48 hours.

7. The effects on other organs cannot be fully estimated but there does not appear to be any ill effect on the patient's general health. She has recovered from the distressing postoperative effects and requires only an occasional follow-up examination. For some unexplained reason, the cephalin flocculation test was positive on two trials. However, her other liver function tests were normal. Complete studies of pancreatic function with secretin stimulation were attempted but were not successful because of the patient's inability to cooperate, but the stool analysis shows no excess fat and no starch. The fasting blood sugars and glucose and galactose tests are normal.

#### SUMMARY

1. An opportunity presented itself to study the effects of subphrenic vagotomy alone over many years on a patient with duodenal ulcer and to note the early and late changes that occurred.

2. Because of the prolonged motility disturbances, it was possible to anticipate that this untoward symptom would occur in the operation of transthoracic vagotomy as a sole procedure in the surgical therapy of gastroduodenal ulcer as advocated by Dragstedt and others.

3. Finally, it seems probable that as a result of subphrenic bilateral vagotomy alone, the acidity and motor response of the stomach was lowered for many years. Vagotomy, although incomplete (as shown by the positive insulin response), may apparently still heal a peptic ulcer, as illustrated in our case, presumably by a decrease in these two factors.

#### CONCLUSIONS

1. A postoperative study of 11 years' duration of a patient who had a subphrenic bilateral vagotomy for duodenal ulcer is presented.

2. A dissociation between the motor and secretory effects following the vagotomy occurred. This has been noted by other observers.

3. The insulin test revealed that the vagotomy was incomplete.

4. The incomplete vagotomy apparently induced a prolonged and a profound motility disturbance with symptoms.

5. The incomplete vagotomy either healed, or at least prevented the recurrence of a duodenal ulcer over a long period of observation (over 11 years to date).

6. Therefore, it is probable that an incomplete vagotomy may lead both to untoward and beneficial effects.

7. There was no definite evidence of an injurious effect of this vagotomy on the other visceral functions.

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THE GASTRIC POUCH FROM ITS ORIGINS TO THE PRESENT  
AN HISTORICAL STUDY IN THE METHODOLOGY OF GASTRIC PHYSIOLOGICAL  
RESEARCH, WITH PARTICULAR REFERENCE TO THE  
CONTRIBUTIONS OF PAVLOV\* †

FRANKLIN HOLLANDER, PH.D.

It is a major principle of research methodology, adhered to rigorously in this Laboratory, that gastrointestinal physiology must be investigated on unoperated animals or on those subjected to an aseptic operation specifically for the purposes of the investigation. In the latter case, sufficient time for complete recovery from the operation itself must be allowed to elapse before performance of the first experiment. The performance of an experiment during laparotomy—using so-called “acute” or “sacrifice”, in contradistinction to “chronic” preparations—is considered invalid for the study of physiological relations, especially those which involve neural mechanisms in all but an occasional situation. Rigid observance of this rule is essential in order to avoid uncontrolled variables in the experiment which arise from anesthesia and trauma. The history of experimental methods employed for the study of the gastrointestinal secretions gives ample evidence of the progressive recognition of the importance of this principle. What is not generally recognized, however, is our profound obligation to the Russian physiologist, Pavlov, for its early formulation, along with that of many other methodological requirements for physiological investigation of the alimentary canal. These principles may well be restated in Pavlov’s own words (20) as a mark of our indebtedness to him for their guidance in our own research activities.

“Our first problem consisted, therefore in the working out of a method. It was necessary to know how the reagents were poured out upon the food brought into the digestive factory. To accomplish this in an ideal manner required the fulfillment of many and difficult conditions. Thus it was necessary to be able to obtain the reagents *at all times*, otherwise important facts might escape us. They must be collected in *absolutely pure condition*, if we were to determine how their compositions varied, and also in *accurately measurable quantities*. Lastly, it was necessary that the *digestive canal should perform its functions normally*, and that the *animal under experiment should be in perfect health*.” (pp. 3-4)

“... it becomes more evident every day that, in the performance of the ordinary so-called “acute” experiment, carried out at one sitting, and complicated by free bleeding, many sources of error lie concealed. The crude damage done to the organism sets up a number of inhibitory influences which react upon the functions of its different parts. The body as a whole, in which an enormous number of different organs are linked together in the most delicate union for the performance of a common and purposive work, cannot in the nature of things remain indifferent to forces calculated to destroy any part of it.” (p. 18)

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\* From the Gastroenterology Research Laboratory, The Mount Sinai Hospital, New York, N. Y.

† Presented at the Seminar on the History of Medicine, The Mount Sinai Hospital, March 28, 1950.

With this introduction to our subject, let us trace the historical development of experimental surgical procedure in gastric physiology in pursuit of this ideal.

The employment of lower animals for the experimental collection of gastric contents first appeared in the literature in 1692, when Viridet is reported to have killed animals specifically for this purpose. The first experimental collection of gastric juice *in vivo* is ascribed to Reaumur (1750), who collected stomach contents from birds with the aid of a sponge attached to a string. About 10 years thereafter, investigations of human gastric juice were initiated by Reuss, specimens being collected from persons who could vomit voluntarily. Because of the crudeness of these methods, the results obtained by means of them have contributed but little to the mass of data collected subsequently by more rigorous procedures.

The first systematic efforts at studying gastric secretion were reported by Beaumont in 1833, who employed his famous patient with an accidentally formed gastric fistula, Alexis St. Martin, as a subject for many years (2). Inspired by the efficacy of the fistula technique thus demonstrated, Bassov (1) and Blondlot (4) independently applied it a decade later to experimental animals, using an indwelling tube and cork to stopper the surgically devised gastrostomy. Concerning this pioneer work, Pavlov (20) wrote,

"This method raised great hopes at first. . . . But, as time went on, the expectations gave place to disappointment. . . . Voices were, therefore, loud in denunciation of the gastric fistula; it had justified none of the hopes, and had proved of little value." (p. 11)

This disillusion was engendered by the extensive contamination of the pure gastric juice with saliva, duodenal contents, and even food residues—such as is usually encountered in collections through a whole stomach fistula.

Now, in 1875, Klemensiewicz (17) had operated on a dog in such a way as to form from the antral wall a vagotomized pouch, completely isolated from the remainder of the stomach and discharging its secretion to the outside through a stoma in the abdominal wall. Unfortunately, this first attempt at preparation of an isolated stomach pouch was unsuccessful since the animal survived only 3 days. A few years later, however, Heidenhain (9) repeated the experiment and this time the attempt was successful. Consequently, as a device for collecting completely uncontaminated gastric juice, he next prepared a similar isolated pouch from the fundus portion of the stomach (10), thus giving us the famous pouch now known by his name (fig. 1). This Heidenhain pouch would seem to satisfy all of the requirements for an auxiliary stomach as regards yielding pure gastric juice and reflecting all the physiological responses of the main stomach—except that it is completely deprived of its innervation from the vagus nerves. Because of Pavlov's concern with neural stimulating mechanisms, this single deficiency constituted a serious experimental handicap in the pursuit of his objectives. During the latter decades of the 19th century, an arduous controversy was going on in European medical circles (and especially Russian) as to whether gross physiological reactions like gastric secretion are influenced by neural stimuli at all. Pavlov and his school were major proponents of the theory of

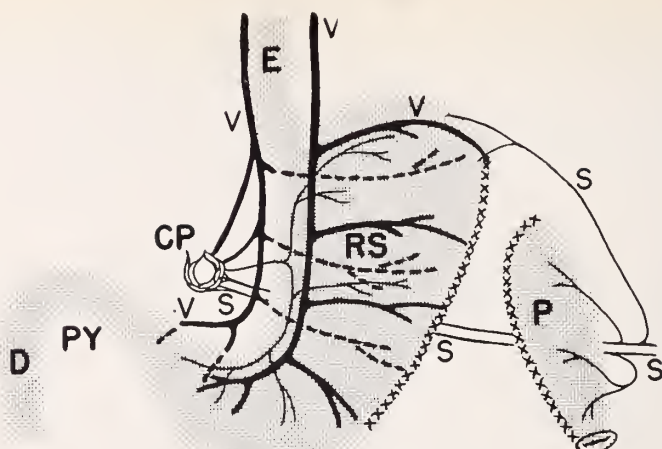


FIG. 1. Heidenhain (vagotomized, corpus) pouch. Diagram showing nerve supply to anterior surface of the stomach and pouch. Dotted lines indicate vagal branches on the posterior surface. The lines of suturing are indicated by crosses.

- CP—celiac plexus
- D—duodenum
- E—esophagus
- P—pouch
- PY—pylorus
- RS—residual stomach
- S—sympathetic nerves
- V—vagus nerves



FIG. 2. Sham feeding dog. Diagram showing gastrostomy and double esophagostomy.

neural control, and their efforts at collecting supportive evidence for it were directed at the several secretory organs of the digestive tract. Experimental procedures for working with the fully innervated pancreas and salivary glands,

including the performance of suitable neurectomies, were relatively simple, but the stomach offered much greater difficulty. In 1895, Pavlov and his student Selumova-Simonovskaia (21) had combined the gastrostomy technique with a double esophagostomy in the dog, and performed the first of the sham feeding experiments which played such an important role in subsequent physiological research (fig. 2). The results of this investigation, to quote Pavlov further:

"... definitely settled the problem of obtaining pure gastric juice ... from a dog almost as milk is obtained from a cow. (However, this method) does not afford us the means of observing the rate of secretion of the juice and of studying its properties during digestion. Obviously, to accomplish this there must be the continuance of normal gastric digestion side by side with a quantitative collection of perfectly pure juice." (pp. 11-12)

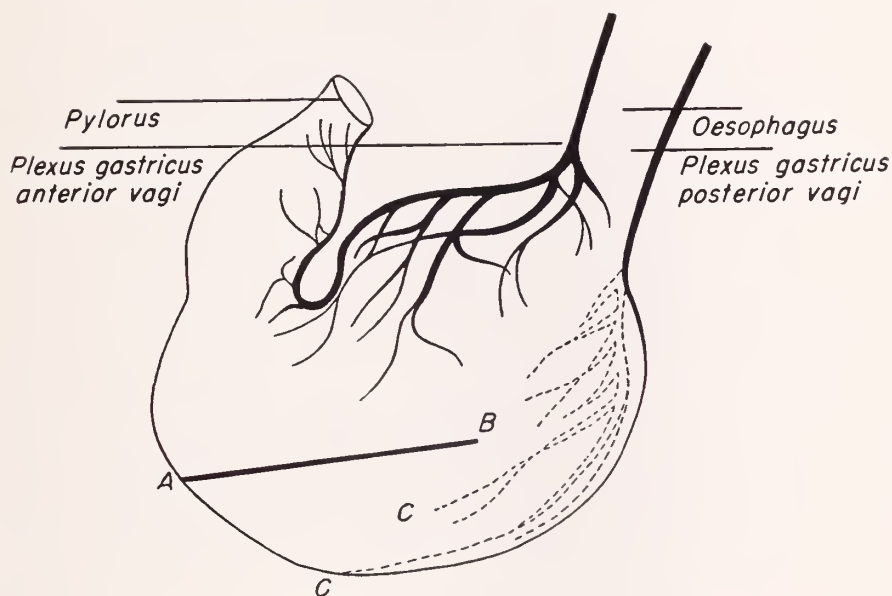


FIG. 3a. Classical diagram for preparation of Pavlov (vagal, corpus) pouch.

A—B—Line of incision

C—Portion of stomach used for the pouch

[From Pavlov: *The Work of the Digestive Glands*. London, Charles Griffin and Co. Ltd., 1910, 2nd Eng. Ed., p. 15]

Having recognized the inadequacy of the gastrostomy-esophagostomy technique for many of his purposes, and the promise afforded by the Heidenhain pouch, Pavlov proceeded to modify the latter in such a way as to make it yield the advantages of both for his ultimate objective. The result was the now famous Pavlov pouch, developed in conjunction with his student, Khizhin (15). The classical diagrams, illustrating the construction of this vagally-innervated corpus or fundus pouch, are presented in Figures 3a and 3b; a photograph of a typical specimen removed at autopsy is shown in Figure 4. According to the original



description of the operation, the successful preparation of this innervated auxiliary stomach was possible because of a major difference in the anatomy of the gastric vagi in the dog and in man—a fundamental point, which has since been disproved conclusively by work in our own Laboratory, and which will be discussed in detail later. In spite of this error in their knowledge of the dog anatomy, however, there is still good reason to believe that the Pavlov pouch reflects all the secretory responses manifested simultaneously by the residual main stomach, and therefore the essential attainment of Pavlov's original objective.

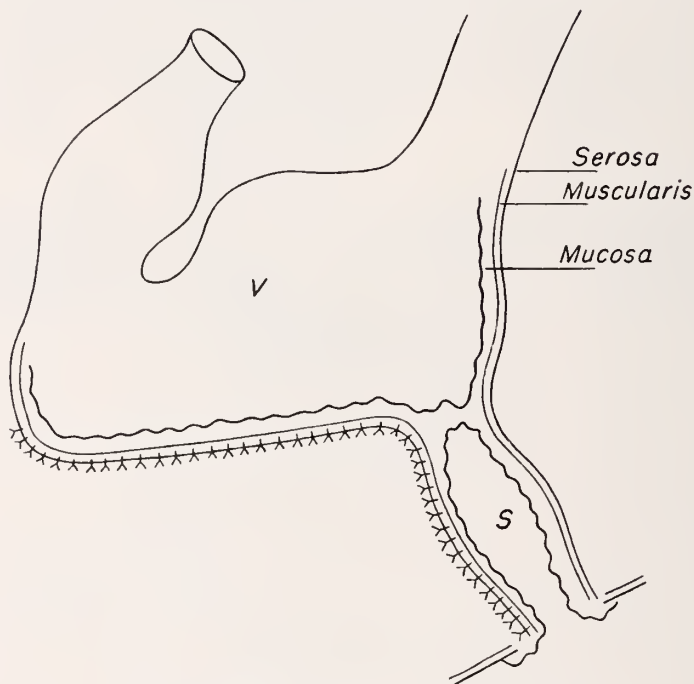


FIG. 3b. Classical diagram of Pavlov pouch

S—pouch

V—residual stomach

[From Pavlov: *The Work of the Digestive Glands*. London, Charles Griffin and Co. Ltd., 1910, 2nd Eng. Ed., p. 17]

Since the beginning of the 20th century, both the Heidenhain and the Pavlov pouches have been used extensively by other investigators. In addition, however, numerous variants of these gastric pouches have been proposed for special purposes not fulfilled by the two classical variants. Thus, in 1906, Lönnqvist (19) extended their experimental usefulness by the simultaneous provision of both a gastric and a duodenal fistula, effected by transection at the pyloro-duodenal junction in a two-stage operation (fig. 5). There is also the completely neu-rectomized pouch described by Bickel and Katsch (3) in 1912. This is essentially the same as the corpus pouch invented by Heidenhain, except that it is deprived

not only of its vagal, but also of its post-ganglionic sympathetic supply, both mesenteric and peri-vascular (fig. 6). Related to this is the celiac-ectomized Heidenhain pouch devised by Lim, Ivy, and McCarthy in 1925 (18), and also prepared in two stages. Deprivation of the mucosa and of its neural supply was extended even further by Eugene Klein at this Hospital, who described (16) an exteriorized preparation made from mucosa and submucosa only, and hence freed even of the intramuscular Auerbach's plexus. In spite of the high digestive activity of the secretion which drains from these various pouches between

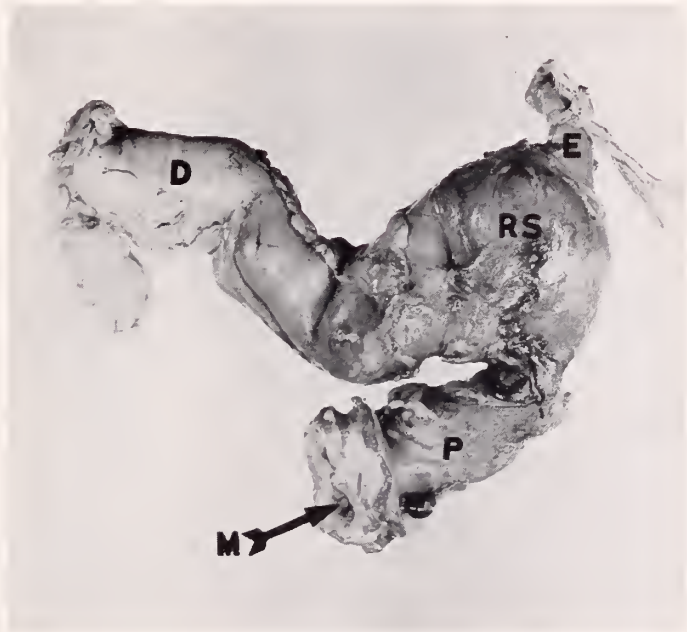


FIG. 4. Specimen of Pavlov pouch

- D—duodenum
- E—esophagus
- M—mucosa of pouch mouth surrounded by portion of abdominal wall
- P—pouch
- RS—residual stomach

experiments, erosion of the abdominal wall about the fistula can be kept at a minimum (fig. 7) with the assistance of a suitably trained and conscientious animal technician. The general state of well-being and contentment of such operated dogs affords strong evidence against the slanderous attacks of antivivisectionists whose efforts have been directed especially against the use of such animals for gastrointestinal research. Modifications in construction of the stoma of a corpus pouch, designed to keep the orifice closed by a functional valve, have been reported by Hollander and Cowgill (11), and by Goldberg and Mann (8). Although neither of these surgical devices has contributed directly to the theoretical development of pouch construction, they have proved of con-

siderable practical help in the care and experimental manipulation of animals with auxiliary stomachs. It may be noted also that variants of the original vagotomized pyloric pouch, described by Klemensiewicz and by Heidenhain, were introduced by Chang and Lim (5). These include complete retention of the vagus supply to the mucosa of the pyloric canal in one case, and its partial retention in another.

In contrast with the auxiliary stomach pouches already mentioned, Lim *et al.* (18) have described a pouch prepared from the entire stomach with esophago-

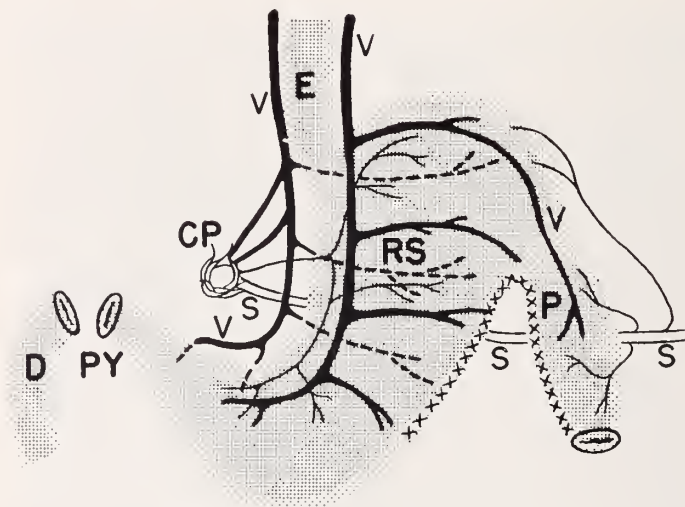


FIG. 5. Lönqvist-Pavlov pouch (vagal, corpus pouch with double duodenostomy). Diagram showing nerve supply to anterior surface of the stomach and pouch. Dotted lines indicate vagal branches on the posterior surface. The lines of suturing are indicated by crosses.

CP—celiac plexus  
D—duodenum  
E—esophagus  
P—pouch  
PY—pylorus  
RS—residual stomach  
S—sympathetic nerves  
V—vagus nerves

duodenal anastomosis and provided with a stoma at the pyloric end (fig. 8). This preparation is vagotomized, but Dragstedt (7) subsequently modified the operation in such a way as to retain the entire gastric vagal supply except for those fibers embedded in the wall of the lower esophagus near its junction with the cardiac portion of the stomach. Pavlov has stated that a similar preparation was made by Frémont, but there is no record of this anywhere else in the literature.

The foregoing reviews the better known variants of the classical pouch technique which have been devised during the last 75 years. Of all these, however,

the Pavlov pouch continues to play a most prominent role in the study of gastric secretion. At no time has there been any reason to doubt the general validity of Pavlov's contention regarding the parallelism between its secretory activity and that of the residual main stomach whether the stimulus be neural or humoral. One finding, however, has raised some question as to whether this parallelism is as truly quantitative as Pavlov believed. It will be recalled from Figure 3 that the Pavlov pouch was designed in an effort to retain all of the vagus nerve supply

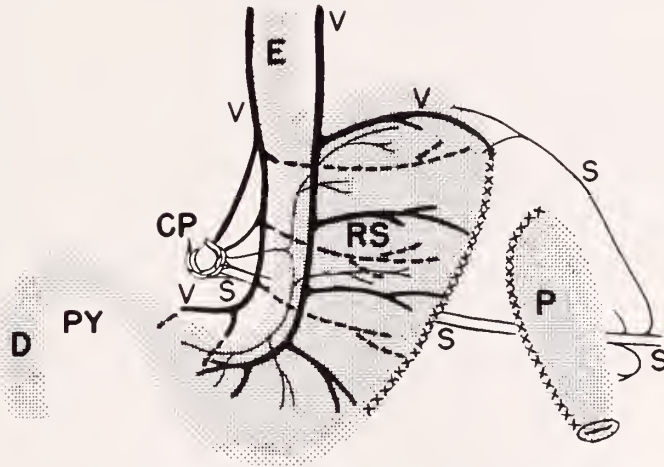


FIG. 6. Bickel (vagotomized and sympathectomized corpus) pouch. Diagram showing nerve supply to anterior surface of the stomach. The pouch has been deprived of its mesenteric and peri-vascular (postganglionic) sympathetic nerves, as well as its vagal branches. Dotted lines indicate vagal branches on the posterior surface. The lines of suturing are indicated by crosses.

- CP—celiac plexus
- D—duodenum
- E—esophagus
- P—pouch
- PY—pylorus
- RS—residual stomach
- S—sympathetic nerves
- V—vagus nerves

which preoperatively innervates the area of gastric wall included in the pouch. This was feasible, according to the original description, because the distribution of the main gastric vagi is different in the dog from that in man. In the latter, the two trunks course symmetrically along the lesser curvature, down to the pyloric antrum. One of these sends branches downward across the posterior wall of the stomach, more or less at right angles to the main trunk; secondary branches penetrate the sero-muscular layer, and their ramifications ultimately become lost in the intra-mural nerve plexus which pervades the entire gastric wall. The other nerve ramifies on the anterior wall in similar manner. In the dog, however, although the posterior vagus is located and distributed as in man, the main





FIG. 7. Mouths of gastric corpus pouches in dogs  
 Left—with exterior mucosal rosette  
 Right—with no exteriorized mucosa

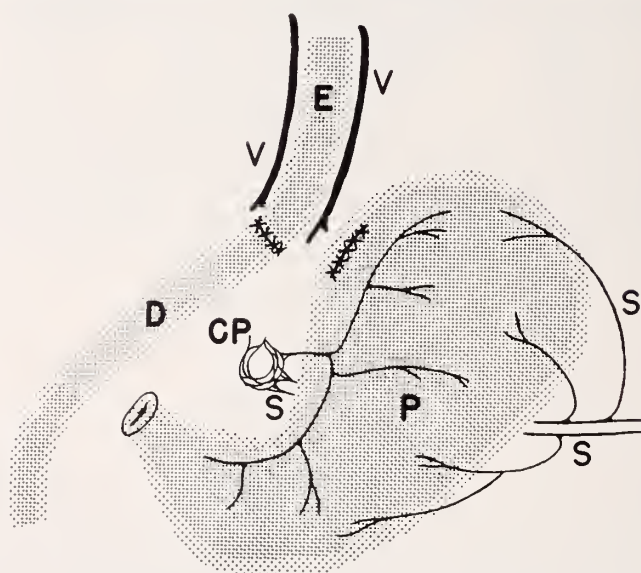


FIG. 8. Whole stomach pouch (vagotomized, but with sympathetic innervation intact). Diagram showing nerve supply to anterior surface of the pouch. Lines of suturing are indicated by crosses. Continuity of the alimentary canal was reestablished by means of an esophago-duodenostomy in the early preparations, but now an esophago-jejunostomy is generally performed.

CP—celiac plexus  
 D—duodenum  
 E—esophagus  
 P—pouch  
 S—sympathetic nerves  
 V—vagus nerves

anterior trunk was thought to be radically different in that, shortly after emerging through the diaphragm, it was believed to pass along the *greater curvature* and send its branches *upward* across the stomach. This is the essence of the description given originally by Khizhin in his doctor's dissertation (15). Because of this difference between the two trunks, the incisions which separate the pouch from



FIG. 9. Specimen of dog's stomach showing both vagal trunks along lesser curvature

A—anterior vagus trunk  
P—posterior vagus trunk  
E—esophagus  
PY—pylorus

The vagi were painted with India ink for visibility.

the main stomach were made to pass between the lesser and the greater curvatures, more or less parallel to the former. As a result, the posterior trunk would remain intact and pass in its entirety through the sero-muscular isthmus between the pouch and the residual stomach, whereas the anterior trunk would similarly continue to innervate the residual stomach. For this reason, Pavlov and Khizhin believed the integrity of the vagus supply to the pouch mucosa was insured in its entirety.

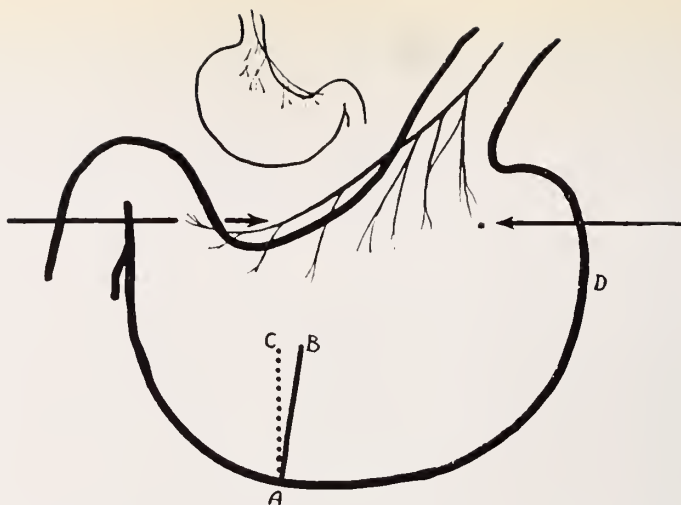


FIG. 10. Hollander-Jemerin (total vagal, corpus) pouch. Diagram of anterior surface of dog's stomach showing direction of initial incisions in relation to course of anterior vagus trunk and branches. Insert shows symmetrical position of posterior vagus.

A—B—initial incision through the anterior gastric wall

A—C—corresponding incision through the posterior gastric wall

D—proximal, fundal limit of pouch

Arrows show approximate position of gastric clamp.

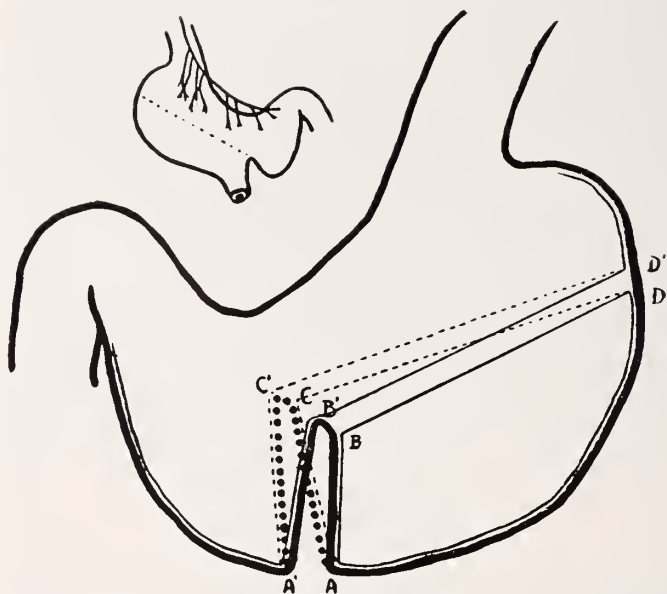


FIG. 11. Hollander-Jemerin (total vagal, corpus) pouch. Diagram illustrating stomach with incisions completed. Fine lines represent mucosa; heavy lines sero-muscular layers. Insert shows completed pouch (posterior aspect) with uninterrupted vagal supply.

AB—edge of incision through all gastric layers; anterior surface; pouch side

AC—edge of incision through all gastric layers; posterior surface; pouch side

A'B' and A'C'—corresponding incision edges on residual stomach side

BD—edge of incision through mucosa only; anterior surface; pouch side

CD—edge of incision through mucosa only; posterior surface; pouch side

B'C' and C'D'—corresponding incision edges on residual stomach side

Reexamination of the vagal anatomy in the dog by Jemerin and Hollander (13), however, revealed an essential error in this neuro-anatomical basis of Pavlov pouch construction. Instead of differing from the human, the transgastric distribution proved to be essentially the same in both species (fig. 9), and what the early workers thought to be the entire posterior trunk was only one or two large branches of it. Consequently, instead of the entire posterior trunk with

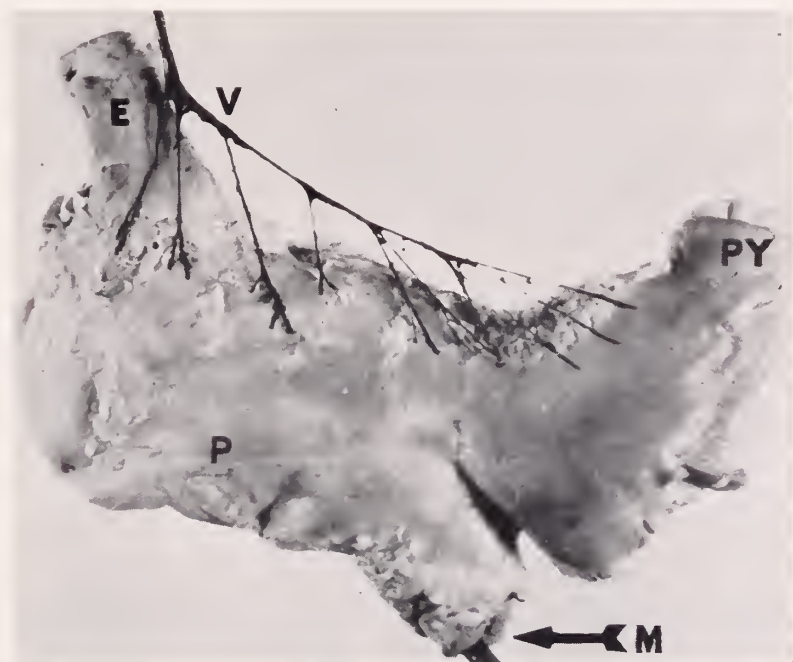


FIG. 12. Specimen of Hollander-Jemerin pouch. Posterior aspect with residual stomach not marked.

- E—esophagus
- M—mouth of pouch with catheter protruding
- P—pouch
- PY—pylorus
- V—posterior vagal trunk

all of its ramifications passing to the pouch mucosa, and the anterior being entirely excluded therefrom, both of the main trunks remain outside the pouch and at least 75% of their branches are transected by the initial incisions across the stomach. In short, instead of being totally innervated as Pavlov and Khizhin believed, their pouch usually retains less than 25% of its essential vagal supply.

Is this anatomical deficiency in vagal supply reflected by a physiological deficiency in secretory activity? This question followed immediately on the discovery that the classical Pavlov pouch is only partially innervated. In order to answer it, Hollander and Jemerin (12) first prepared a corpus pouch of their own, one in which nearly all of the vagal branches which course to the pouch mucosa



preoperatively are left intact after the operation. Diagrams to illustrate the surgical manipulation of the stomach required for this purpose are shown in Figures 10 and 11, and a photograph of one such preparation is given in Figure 12. The fact that the typical Pavlov pouch is only partially innervated is now generally recognized, and techniques for preparing total vagal pouches have been described by Cope *et al.* (6) and by Thomas (22), as well as ourselves. Although use has already been made of such completely innervated pouches, the fundamental question regarding quantitative differences between their responses to stimulation of the vagus center and the responses of the partially innervated Pavlov pouch still remains to be investigated. As a next step in this direction, a test procedure has been developed in this Laboratory (14), based on the intravenous injection of sufficient insulin to depress the blood sugar to 50 mg./100 ml. or less, and the output of gastric juice in response to central stimulation by such an adequate hypoglycemia. Further pursuit of this and related problems is now being contemplated.

Thus, the more important steps in the development of the pouch technique have been traced from its pre-history up to the present time. The many varieties of auxiliary stomach which have been devised, and the widespread use which has been made of such chronic dog preparations in preference to the acute variety, give ample evidence of the importance which physiological investigations attach to them. For a clear formulation of the principle that gastrointestinal physiology must be investigated on animals which are generally healthy, we owe a tremendous debt to the great leader and pioneer, Professor I. P. Pavlov.

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## MALROTATION OF THE INTESTINE

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Intestinal obstruction is often due to congenital anomalies which usually produce symptoms within a short time after birth. However, they may exist without complaints until adult life before they become troublesome. This discussion will be limited to the extrinsic lesions involving the midgut which result from abnormalities of intestinal rotation. More common obstructing pathologic conditions are: pyloric stenosis, intussusception, obstructions about the anus and rectum, incarcerated inguinal hernia, atresia of the oesophagus or of the small intestine, duplication of the intestine, meconium ileus, etc.

A clear picture of the embryological development of the intestine is an aid to the surgeon when a bewildering mass of small intestines confronts him at operation. He can better unravel the various derangements, abnormal positions, and unusual fixations of the midgut. The foregut and hindgut remain relatively fixed during their early stages; so that their abnormalities of position are exceedingly rare. In contrast to this, irregularities are quite frequent in the midgut because it normally undergoes complicated rotations and maneuvers before it arrives at what is considered the normal adult anatomical position. The foregut is that part of the embryonic alimentary tract cephalad to about the middle of the second part of the duodenum. The coeliac axis is its blood supply. The hindgut extends from just past the middle of the transverse colon to the rectum, and it is supplied by the inferior mesenteric artery. The midgut is loosely suspended as a loop from its relatively fixed upper and lower portions. It is supplied entirely by the superior mesenteric artery. The intestine develops from the yolk sac, or endodermic vesicle.

At about the fourth week of embryonic life, the tubular, primitive, alimentary tract extends down the sagittal plane and it is suspended by a common dorsal mesentery. It has a round lumen lined by epithelial cells. The anterior mesentery persists only in the foregut. At the end of the fourth week, the midgut grows rapidly: it elongates and there is a proliferation of its epithelial cells to completely obturate the lumen. The available intraabdominal space has been further diminished by the enlarging liver; so that the midgut protrudes into the base of the umbilical cord. This extra-embryonic portion of the celom is often called the umbilical celom. The yolk sac is extracoelomic, and it is connected to the midgut by an elongated narrow tube which is variously called the yolk stalk, vitelline duct or omphalomesenteric duct. The yolk sac normally loses its connection with the intestine at about 5 to 6 weeks (7 mm. embryo), and the yolk duct degenerates. This time is not constant, for the sac may be present even in an embryo of 12.5 mm. The omphalomesenteric vein and artery accompany the duct. Generally, the vessels remain a little longer than the duct. Should the latter persist to some extent after birth, it is eponymed Meckel's diverticulum. The

mass of cells which had proliferated into the lumen of the intestine has, by this time, disappeared to reestablish the tubular form. The closure of the abdominal wall to and around the umbilicus is relatively complete by the twelfth week. The growth and approximation involves the ectoderm (epidermis) and mesoderm (derma, muscle, fascia and peritoneum).

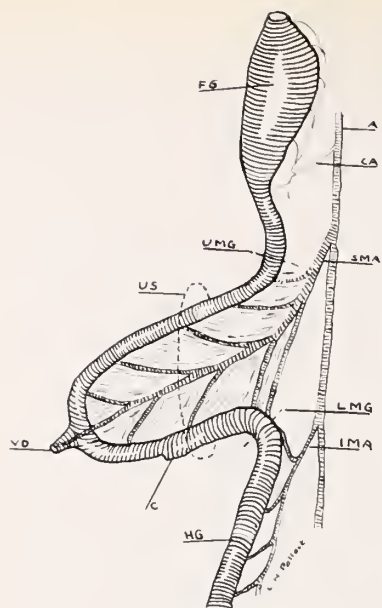
The greater curvature of the stomach is formed by the enlargement of the posterior portion of its anlage in the foregut. This turns to the left while the first part of the duodenum rotates to the right, becoming fixed to the posterior coelomic wall. The ventral mesentery shortens and the pancreatic rudiment develops, which helps immobilize the lower part of the foregut. The upper portion of the hindgut becomes relatively attached by a decreased growth of its mesentery which passes up to the origin of the superior mesenteric artery. As the abdominal cavity enlarges, the fixed upper portion and the fixed lower end of the midgut are thus quite close together: the midgut hangs in a "U" shape from this narrow duodenocolic isthmus about which the fetal rotation develops.

As the midgut lies in the umbilical root, it rotates from its sagittal to a transverse position, with the prearterial portion to the right and the postarterial segment to the left. The part proximal to the vitelline duct and artery is termed the prearterial or descending segment; while that reced to this point is called the postarterial or ascending segment of the midgut. The major part of the rotation occurs very quickly during the 10th week. The proximal segment is thought to return first to the abdominal cavity and it reenters to the right and posterior to the superior mesenteric artery. The cecum and ascending colon are held anteriorly in the physiological umbilical hernia. As the subsequent loops of lower midgut enter the abdomen, the enlarged liver forces them to the left, then down to the right. Thus, the midgut is rotated in a 270 degrees counterclockwise direction behind the superior mesenteric artery from its original sagittal position. The hindgut, with its mesentery, is displaced from the midline up, back, and to the left; thus placing the splenic flexure and the descending colon in its adult normal position. The cecum and ascending colon return last to the abdomen, placing the transverse colon anterior to the root of the mesentery of the small intestine.

Some (10) feel that the cecum does not descend into the lower right quadrant: it is early fixed in its definitive position and appears to descend as further relative decrease in liver size causes this organ to fill only the right upper quadrant of the enlarging abdominal cavity. Others (2) think that the cecum elongates and descends from its subhepatic position to its final location. This is completed about the time of birth, or shortly afterwards. Meanwhile, there has been a fusion of the base of the mesentery of the small intestine to the posterior abdominal wall. It passes down and to the right to form a line of attachment about 6 inches long. The mesentery fans out from this broad base to the small intestine, which is about 20 feet long in the adult. The absence of this wide, oblique attachment predisposes to volvulus of the entire small intestine. The mesentery of the cecum and ascending colon, and that of the descending colon, fuses with the posterior peritoneum to stabilize these parts.

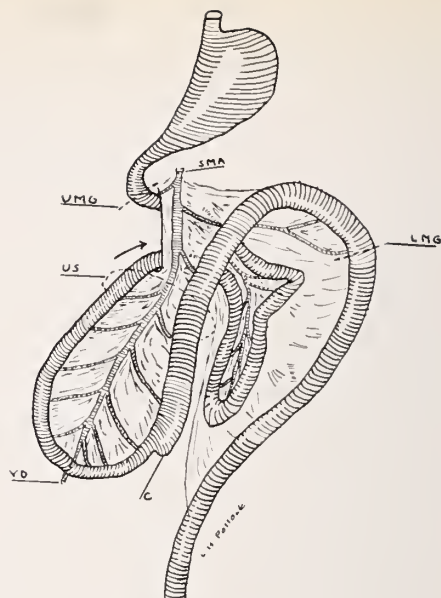
There are two types of derangements which may develop from a congenital





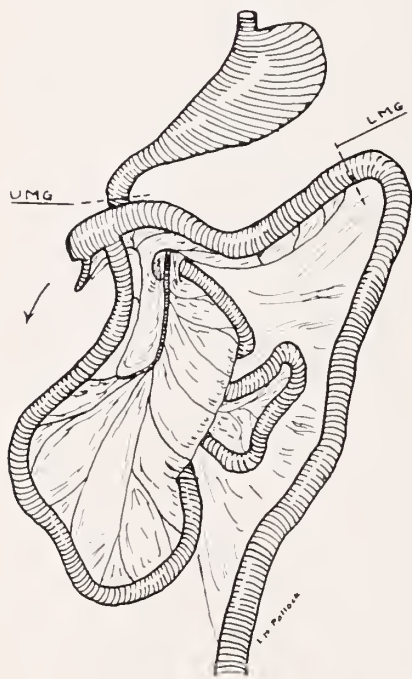
LATERAL

1A

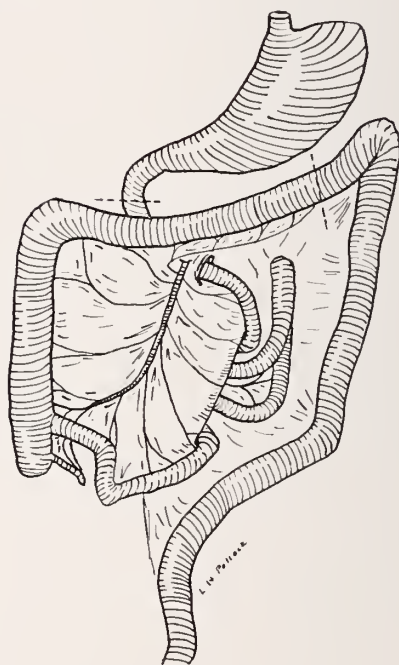


FRONT

1B



1C



1D

FIG. 1 A-D.

origin: (1) partial or complete failure of the intestine to rotate in an orderly fashion; (2) failure of the mesentery to fuse properly.

The small intestine may fail to develop beyond its early occupancy of the root of the umbilical cord. This is associated with a persistence of umbilical membranes, which results in a condition known as exomphalos or omphalocoele. There is a herniation of the intestines which is not covered by skin, as in the usual umbilical hernia, but by a thin, membranous layer which represents the stretched out coverings of the umbilical cord and peritoneum. The sac contains the nonrotated midgut such as seen in the eighth or ninth week.

Nonrotation signifies a failure of the midgut to rotate beyond the extent in the embryo of the 8th week. The duodenum is anterior to the superior mesenteric artery. The normal curve to the left of the third part is absent. Instead, the duodenum passed downwards and to the right of the artery. Very often, the lower half is not fused to the posterior abdominal wall, but has a free mesentery. The small intestine lies in the right side and the colon in the left side of the abdomen. The terminal ileum passes across to the left and enters the left-sided cecum from the right, instead of from the left as seen in the normal individual. The ascending colon passes upwards to the splenic flexure behind the stomach. There may be a failure of fixation of the mesentery extending from the mid-duodenum to the splenic flexure of the colon. Volvulus of the entire midgut occurred in 41 out of 88 cases of total volvulus studied in the literature by Gardner-Hart (2).

Malrotation is the designation of imperfect development of rotation or fixation. In one form, the prearterial segment rotates normally behind the superior mesenteric artery. Meanwhile, the cecum has rotated to some extent, becoming arrested in the epigastrium, or in the upper right quadrant. In this form, the first part of the colon and cecum may be fixed by peritoneal bands which extend to the subhepatic area or to the right lateral gutter. These overlie and compress the duodenum or pylorus to cause obstruction of varying degrees. The common

FIG. 1. Schematic diagram of the normal development and rotation of the midgut in the embryo. The upper and lower extremities of the midgut are indicated by the dotted lines in the middle of the duodenum and the midtransverse colon, respectively.

A—Aorta; C—Cecum; CA—Coeliac Axis; FG—Foregut; HG—Hindgut; IMA—Inferior Mesenteric Artery; LMG—Lower end of Midgut; SMA—Superior Mesenteric Artery; UMG—Upper end of Midgut; US—Umbilical Stoma; VD—Vitelline Duct.

A. Fifth week of fetal life. Lateral View. The foregut, midgut, and hindgut are pictured with their respective blood supply. They are supported by their common dorsal mesentery in the sagittal plane. Most of the midgut protrudes into the base of the umbilical cord where it normally remains from the 5th to the 10th week.

B. Tenth week of fetal life. Anterior View. The intestine rotated from the sagittal plane to the transverse plane during the 8th week, constituting the first stage of rotation. In the early part of the 10th week, the intestines elongate and the hindgut is shifted to the left side of the abdomen. The upper part of the small intestine is in the process of reentering the abdomen from the root of the umbilical cord. The proximal segment passes behind the superior mesenteric artery. During the 10th week, the rest of the small intestine progressively enters the abdominal cavity behind the artery. Thus the midgut rotates 270 degrees in a counterclockwise direction from its original sagittal position.

C. Eleventh week of fetal life. Anterior View. At the end of the second stage of rotation, the cecum lies in the right upper quadrant of the abdomen.

D. Rotation of the colon is completed just about the time of birth or shortly afterwards. The cecum lies in its definitive position.

bile duct may be compressed to give biliary obstruction. If the first half of the colon has a mobile mesentery, this predisposes to volvulus of the cecum and terminal ileum in the upper abdomen. In another type, the small intestine remains on the right side and the postarterial segment rotates normally. However, the latter has not been able to become fixed to the posterior parietes because of the small intestine. The cecum, ascending colon and small intestine have a common and continuous mesentery. Some degree of volvulus may compress the duodenum and cause dyspepsia symptoms.

Reversed rotation of the midgut may occur in which it undergoes a 90 degrees clockwise instead of the usual 270 degrees counterclockwise rotation. Thus, the lower duodenum and jejunum and superior mesenteric artery pass anterior to the first half of the colon. Ten cases have been reported (2) in which the mesentery of the ascending colon has been partially fixed in the right lateral gutter; while the hepatic flexure portion and transverse colon pass posterior to the small intestine and become fixed in a tunnel through the acquired attachment of the upper part of the small intestine.

Failure of the ascending mesocolon to fuse with the posterior parietes results in a peritoneal pocket between these structures. A right lateral gutter hernia is formed when the cecum or proximal intestine enter this space.

#### SYMPTOMS

Errors in rotation may be present without symptoms, only to be recognized incidentally during operations on extraintestinal organs, at autopsy, or during roentgen examination. Of the 105 cases collected by Gardner-Hart, 70 had major defects in intestinal rotation without symptoms. Frequently, the patient may complain of recurrent or chronic gastrointestinal disturbances, such as intermittent pain, with or without vomiting or distention. They may be thought to be nervous or to have gastrointestinal allergy, celiac disease, cyclic vomiting or malnourishment. Some patients with malrotations have trouble in the first few days of life; while others may get by for months or years. The presence of an abnormally rotated intestine, without any symptoms, does not indicate that operation need be performed.

In malrotation of the cecum, it is usually fixed in the epigastrium or right upper quadrant. It has peritoneal bands and membranes which pass to the subhepatic or right lateral gutter areas. These compress the duodenum, or the common bile duct and cause complaints due to obstruction of these organs. The signs and symptoms are due to the obstruction; so that the findings may be indistinguishable from volvulus, intestinal stenosis or atresia. Obstruction from malrotation or midgut volvulus always takes place first at the duodenum. The first symptom is vomiting, and the vomitus usually contains bile. Practically all duodenal obstructions take place below the ampulla of Vater. If the obstruction is complete, the vomiting will be regular, the baby bringing up all food that is eaten. In addition, there will be bile stained vomitus of gastric juices. In partial obstruction, some of the food will pass down; so that the vomiting may be only intermittent.

In volvulus with symptoms only of acute duodenal obstruction, the closure may be partial, intermittent or complete. The newborn seems apparently normal, and the first feedings are taken well for about three or four days. Vomiting then starts about 30 minutes after eating—it is projectile, persistent, and usually contains bile.

Abdominal distention is absent in early obstruction. In fact, when the patient vomits and empties his proximal duodenum, the abdomen is usually flat or scaphoid. Since the lower end of the duodenum and intestines are open, there is no lower abdominal distention. In partial obstruction when the duodenum and stomach have had time to dilate, some distention may be seen in the epigastrium. In volvulus, as it rotates past 180 to 360 degrees, or more, another obstruction occurs in the transverse colon. If the twist is not tight, the lumen may not be completely compressed; so that the loop may remain collapsed. If the twist obstructs both extremities of the loop, or if the blood supply is occluded, the closed loop becomes distended and may be gangrenous. Thus, later, there may be soft midabdominal distention.

Evidence of pain, such as crying, and vomiting are thus the most common indications of intestinal obstruction. Visible duodenal and gastric peristalsis may be present in chronic or recurrent obstruction. Blood stained fluid may be passed rectally to indicate vascular involvement. Melena may be due to mesenteric and intramural varices produced by chronic obstruction to venous return from malpositioned bowel.

The passage of meconium in the newborn is no assurance of the absence of complete intestinal obstruction. It may be formed below the site of occlusion. Examination of the meconium stool may help one determine if the obstruction is an atresia or otherwise complete. Analysis of a normal specimen will reveal (a) squamous epithelial cells which represent the vernix caseosa desquamated from the fetus's skin and which the fetus has swallowed; (b) epithelial cells from the intestinal lining, etc. When there is a complete obstruction, the swallowed amniotic fluid obviously will not pass; so that these cornified cells will not appear in the meconium. A portion of the center of the stool is spread on a slide. It is washed with ether to extract the fat and is then dried. It is stained for a minute with Sterling's gentian violet, washed with running water, and decolorized with acid alcohol which removes the stain from all the cells except the cornified epithelial cells. The complete absence of deeply stained cornified squamous epithelial cells is presumptive evidence that there is an intestinal obstruction. However, if a moderate number of cells are seen, the obstruction may be only partial, as intestinal stenosis or due to extrinsic pressure.

Acidosis and dehydration may rapidly become evident.

Volvulus with recurrent or partial duodenal obstruction may cause intermittent attacks until late adult life. The history usually dates back as far as the patient can recall, having episodes of epigastric discomfort, pain, vomiting, with or without some epigastric distention. There usually is constipation. The vomitus is profuse, bile-stained, and may have particles of food eaten several hours before. The patient may become malnourished and emaciated.



If the volvulus involves only parts of the small intestine, the acute form causes symptoms similar to those of obstruction from any cause. There is sudden onset of intestinal cramps, vomiting, distention, and constipation. Collapse and death may result in a few hours.

When the cecum is fixed high, an important physical finding is the emptiness of the lower right quadrant. Pressure there does not yield the usual fullness and feeling of gas in the cecum.

#### DIFFERENTIAL DIAGNOSIS

*Pyloric stenosis* is the most common cause of intestinal obstruction in infancy. Its ratio in the male compared to the female is reported to be as high as 85:15. The first and most common feature is vomiting which usually starts about the 10th to 14th day of life. At first, it may be only a regurgitation. It may almost stop for two or three days with only occasional vomiting, but it becomes progressively worse until almost all food is vomited. Sometimes, the volume vomited is greater than the previous feeding because of gastric secretion and retention. It usually comes comparatively soon after ingesting milk and it is explosive in character. The vomitus is never bile-stained, but it may contain mucus or blood due to the associated gastritis or rupture of a mucosal vessel. Visible peristalsis are seen running from left to right in the epigastrium. Sometimes, the stomach outline is visible through the thin abdominal wall. A pyloric tumor is palpated. There is loss of weight, dehydration and scanty stools rather than impaction. There is no relief with sedatives or antispasmodics. Distention, if present, is limited to the upper abdomen. Roentgen examination reveals long gastric retention and a narrowed and elongated pyloric canal.

*Pylorospasm* usually starts between 10 days and 2 months after birth. There is apt to be periodicity of symptoms: they are worse for a few days and then they appear to get better, only to get worse again. There usually is prompt relief with sedatives and antispasmodics. Roentgen examination shows the spasm.

*Intussusception* occurs somewhat later in life, usually about the 6th or 7th month. It happens quite often in well developed and nourished children (7). It starts suddenly: a baby who is perfectly well one minute, screams with pain the next, turns pale, sweats, and may vomit soon afterwards. These paroxysms usually last 1 or 2 or even 15 minutes. Between attacks, the child may play or go to sleep without discomfort. A small infant may cry and flex his thighs. When the spells recur soon, the child may vomit only stomach contents. The first stool usually is normal since it lay in the sigmoid or rectum. Later, the stools may contain mucus, mucus and blood, or free blood. When seen early between attacks, the child's healthy appearance may cause one to question the parent's concern. The late signs are palpable tumor, general abdominal distention, and bloody stools. The blood may be seen within 4 or 5 hours after the onset of the attack, but may not appear for 10 hours. The examining finger rectally may feel the advancing point much as if feeling a cervix. There may be audible peristalsis. The mass may be poorly defined, but it usually is a definite, rounded or elliptical tumor. It is rather firm and usually not tender. In chronic or subacute forms of

intussusception, pain is less prominent, but usually is the chief complaint. Blood is often absent from the stools.

*Incarcerated inguinal hernia* usually occurs in the first 18 months of life. The presence of the inguinal mass is usually evident for diagnosis.

*Atresia, or stenosis of the intestine:* If the lumen of the bowel is completely occluded, it is called atresia; if it is incompletely occluded or narrowed, it is termed stenosis. During the 4th or 5th week of embryonic life, the epithelial lining of the alimentary tract proliferates so that the lumen is closed by a solid obturator of cells. Later, vacuoles appear, which coalesce to reestablish the lumen of the intestine. This recanalization may fail to develop fully at one or more sites to cause the following varieties of congenital defects: (1) lesser degrees of retarded tubulation results in a segment of bowel of diminished caliber, called stenosis; (2) there may be a diaphragm or veil which is perforated, or a shelf may be present; (3) a nonperforated diaphragm may cause complete occlusion; (4) it may result in a blind sac completely interrupted from the blind beginning of the distal intestine; (5) a string-like band along the free border of the mesentery stretching between the widely separated ends of patent intestine may be present; (6) ends of intestine may be separated with an associated defect in the mesentery. Atresias are more common in the ileum; stenoses are found more frequently in the duodenum. Congenital occlusion of the small intestine occurs in three common sites: the second part of the duodenum, the duodenojejunal junction and the lower ileum. Atresias become evident in the first few days of life by symptoms of complete intestinal obstruction. Stenosis may easily give symptoms of similar degree if the lumen is too small. However, they may not be symptomatic until some precipitating factor as solid foods transform the partial obstruction into a complete one.

*Meconium ileus* is due to obstruction of the bowel by putty-like and adherent meconium which cannot be propelled along the intestine. This disease is associated with pancreatic fibrosis and absence or diminution of pancreatic secretion. The lumen may be further decreased by resultant spasm of the wall. The symptoms are those of acute intestinal obstruction just a day or two after birth. The proximal distention may be marked enough to cause a perforation. The treatment of choice is to expose the involved intestine and irrigate it with pancreatic extracts and saline to liberate and dilute the inspissated meconium.

*Annular pancreas* is very rare. The organ completely encircles the duodenum and produces various degrees of compression. It is due to a persistence of the left half of the ventral anlage of the pancreas which usually disappears. The chief symptoms and signs are those of high intestinal obstruction.

*Superior mesenteric artery syndrome* (chronic duodenal stasis) is seen in the adult. There is partial obstruction of the third part of the duodenum due to pressure by the superior mesenteric artery. This results in dilatation and stasis in the proximal part of the duodenum. The patients usually are of the visceroprotic and lordosis type. This is accompanied by symptoms of chronic epigastric distress, regurgitation or vomiting of food eaten several hours before, and recurrent pain. The roentgenogram shows the dilated duodenum proximal to the artery,

associated with visceroptosis. The general normal disposition of the rest of the intestine would indicate that the pressure is not due to compressing peritoneal bands such as seen in malrotation.

*Peritoneal bands* may cause obstruction by compression or distortion of the intestine which may or may not be malpositioned. The abnormal position, in itself, may in no way impede the passage of its contents through its lumen.

#### ROENTGEN EXAMINATION

Roentgen examination is of the greatest help in arriving at a diagnosis. Erect frontal and lateral views of the abdomen are generally adequate to show complete obstruction. Additional plates may be taken with the patient held upside down. The ingestion of barium is not only dangerous in that it may be vomited or aspirated, but it can convert a partial obstruction into a complete one. It also may delay the necessary surgery. Roentgenograms show the dilatation of the intestine above the obstruction. If the obstruction is in the lower duodenum, the proximal portion and the stomach may be greatly distended to fill the whole upper abdomen. The intestine below is collapsed; so there is an absence of air, producing a homogeneous density in the lower abdomen and pelvis. If the obstruction is in the small intestine, the proximal loops will be distended with air and show fluid levels. Below it, there will be no gas. However, incomplete obstruction can never be excluded when air is present throughout the bowel. Air may pass through apertures which impede fluids or solids, or may pass an intermittent complete obstruction during periods when it is incomplete (10). In acute obstruction, the surgical exposure is the same for all types of lesions. The information gained from a barium enema is not enough to justify the time and trouble required to do it.

When there are chronic, indefinite symptoms, barium enema is a most valuable single procedure. Malposition of the cecum, or abnormal mobility of the cecum, might indicate that there are other abnormalities extant such as compressing peritoneal bands, volvulus, or pressure of other organs. A freely moveable cecum in normal position is as significant as an abnormally located cecum. When gastrointestinal series are taken for subacute or chronic complaints, it may be performed when the obstruction is not in effect. The examination may reveal no abnormality unless definite malposition of the cecum is seen.

#### ETIOLOGY

The etiology of intestinal malrotation, as well as of other anomalies, is unknown. Of the 105 cases (2), 62% occurred in males. The ratio of males is much higher in the other lesions which must be considered in the differential diagnosis. Kiskadden (5) reports males and females to be equally affected by general congenital deformities. Syphilis plays little or no role in the production of these defects. The study of causal embryology shows that the development of the normal adult structure of the separate organs and tissues of the body is a step-by-step process. Each organ originates from a definite embryonic area and from no other. Also, it arises at a very definite moment which must be utilized at that

time and no other. There is an orderly progression of development: there is a chain of inductive reactions where each stage of development is dependent upon the normal completion of the phase immediately preceding it. In malrotation, there is an unknown interruption in the orderly development so that the midgut remains in its unrotated or interrupted partial stage. When there is an omphalo-coele present, one cannot say that this is due to the failure of the midgut to rotate. Nor is the converse true. It is obvious, however, that the sequence of development was stopped at the same embryological level for both the umbilicus and the midgut.

It is common to have other defects associated with intestinal anomalies. A common accompaniment is mental deficiency. It is disturbing to save an infant, only to learn later that it was mentally defective. Other anomalies which may also be present are enteric or mesenteric cysts, persistent embryological umbilical structures as urachus fistula or portion of the vitelline duct; congenital absence of one of the bones, imperforate anus, congenital heart defects, or oesophageal atresia, etc.

#### PREOPERATIVE TREATMENT

The pre- and postoperative care of the child requires diligent care by both the pediatrician and surgeon. In preparation for operation on the acutely obstructed child, everything must be done to improve his condition if it is poor. To help decompress the stomach, increase its tonicity and to avoid the aspiration of vomitus, a soft rubber #8 or #10 urethral catheter can be passed through the nose or mouth. It may also be used for injecting thin barium into the stomach for roentgen study, and then washing it out. In practically all cases, it is best to administer as much parenteral fluid as will be absorbed before operation. Intravenous fluids (10 cc. of 10% glucose per pound of body weight) and saline solution subcutaneously (2½% glucose in Ringer's solution—15 cc. per pound body weight) with alidase are used. Blood is not always given, but it may be life saving and may combat existing bleeding tendency. Vitamin K subcutaneously, 2 mg. daily, and penicillin are given prior to operation. During operation, the young patient is wrapped with cotton batting to cover the extremities and chest. A warm water bottle under the lower back helps keep him warm. Atropine without morphine is given preoperatively,  $\frac{1}{1000}$  grain for patients under 1 year of age;  $\frac{1}{500}$  grain for those between 1 and 2 years; and proportionately higher doses for older ones. No matter how good the condition of the patient, surgery should not be started until fluids are running into a vein or bone marrow. The surgeon and anesthetist may become so engrossed in unravelling the anomalous intestine that a vein may not be found if needed in a hurry.

After operation, it is best to take the child to a private room where there is constant temperature control. All visitors are prohibited to protect him from infection. The head of the bed is elevated about 20 degrees especially during oral feedings. Fluids are administered routinely. For the first day, or as long as there is vomiting, parenteral fluids are given twice daily until dehydration is overcome and adequate fluid can be taken orally. Glucose (5%) may be given by rectal



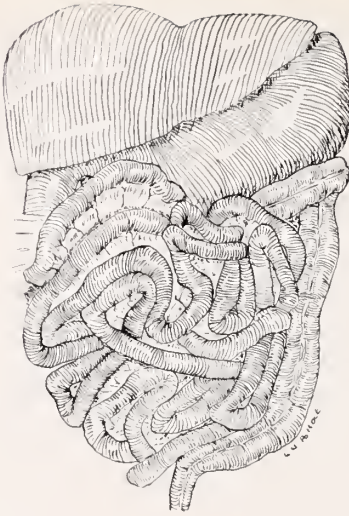


FIG. 2A

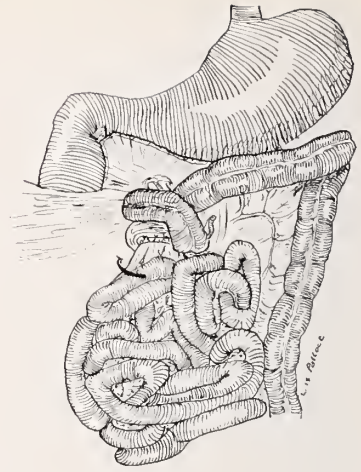


FIG. 2B

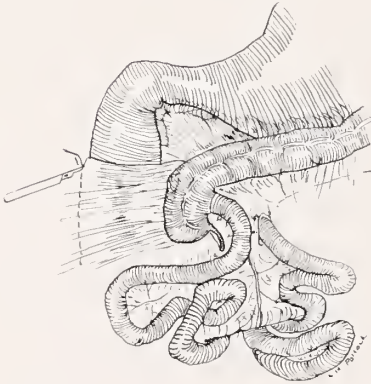


FIG. 2C

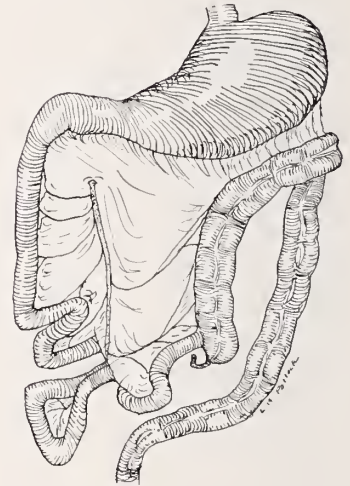


FIG. 2D

FIG. 2. Volvulus of the midgut. Operative treatment of acute intestinal obstruction due to torsion, associated with an incompletely rotated cecum and peritoneal membranes obstructing the duodenum.

A. The appearance of the intestines on opening the abdomen. A mass of small intestine is seen hiding the right colon. The left colon is in its proper position. The intestine may be dusky in color, cyanotic, or gangrenous.

B. The intestinal mass is delivered out of the incision and is pulled downward and to the left to expose the root of the mesentery. There is a volvulus in a clockwise direction of 360 degrees about the imperfectly anchored mesenteric base. The terminal ileum and cecum are twisted about the superior mesenteric artery. The descending duodenum and stomach

drip during the first day and 40 cc. citrated blood transfusion may be given intravenously, followed by 250 cc. of 5% glucose in Ringer's solution. While bone marrow infusions and transfusions may have some danger, this route offers a convenient and rapid method of administration. Earliest tube feedings of protein hydrolysates, whiskey, and breast milk in 2 oz. amounts and pancreatin  $\frac{1}{4}$  grain doses are given.

Vitamin K, 2 mg. daily, and vitamin B and C are helpful. Because of its low toxicity, and ready tolerance, penicillin is a good antibiotic. It is given 20,000 units every 4 hours to help combat infection, peritonitis, and pneumonia. Streptomycin is helpful when there is possibility of infection by colon contents. Oxygen tent may be used. Usually, the full caloric or volume intake for the age and weight are not given until about the 4th or 5th day.

Dehydration, shock, and toxicity account for a majority of postoperative deaths. Peritonitis and pneumonia may occur; and impending evisceration or actual wound rupture as late as the 10th or 12th day. Sometimes, diarrhea may develop during convalescence from infection of the tract or due to operative handling of the intestines.

#### OPERATION

Surgery is performed after adequate preparation of the patient. The indwelling gastric tube is left in—and an intravenous started. The anesthetic of choice is probably the one which the anesthetist can give best. Many prefer drop ether with local infiltration of the abdominal wall with procaine,  $\frac{1}{2}$  to 1%. However, some believe that the debilitated infants do not tolerate ether well because it may irritate the bronchi to form thick mucus. This predisposed it to pulmonary complications. Local procaine, with a sugar tit, augmented with a small amount of ether usually is effective for local procedures as hypertrophic pyloric stenosis but does not usually give enough relaxation for extensive exploration. Experts in pediatric anesthesia effectively use cyclopropane or intravenous pentothal supplemented with curare.

A right rectus incision, starting in the midabdomen, must be adequate enough to explore the whole intestinal tract regardless of the tentative diagnosis or the conceived ease of performance. The surgeon must keep in mind that the obstruc-

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are dilated above the compressing bands from the cecum to the subhepatic area. The volvulus is reduced by turning it en masse in a counterclockwise direction, as indicated by the arrow.

C. The cecum is seen in the epigastrium after untwisting the volvulus. The peritoneal bands compressing the duodenum are visible.

This is also the picture when there is a duodenal obstruction by peritoneal bands with a malrotated cecum, without a complicating volvulus.

The extrinsic duodenal obstruction is released by cutting the peritoneal membranes along the dotted line in the right lateral gutter and subhepatic area. These membranes do not carry any blood supply to the cecum.

D. Disposition of the intestines at the end of the operation. The duodenum has been exposed and straightened out to empty vertically into the jejunum. This is accomplished by dividing its peritoneal attachments, including the ligament of Treitz (if any), to eliminate any kink in the duodenum.

This is also the picture when the intestine is found in a nonrotated position in the adult. Small bowel occupies the right side of the abdomen; while the colon lies in the left side. The terminal ileum crosses the abdomen to empty into the cecum on its right border.

tion quite often may not be due to a single anomaly. The duodenum may have not only incomplete rotation and congenital bands, but may also have a co-existent atresia or stenosis close by or in the lower intestine. To correct one of them, and to fail to relieve another concomitant one because of failure to look for it, or to recognize it, is a common failure in reported cases. One may hope for the easiest, but be prepared for the worst.

On opening the abdomen, there may be a large amount of clear peritoneal fluid. If there is free gas, or if the fluid is cloudy or malodorous, one must rule out an intestinal perforation. The most likely point of perforation is the ileum, and the next frequent is the second part of the duodenum (3). If the small intestine is dilated, it must be inspected for the perforation. If it is collapsed, and the duodenum and stomach have been dilated, the perforation may be in the duodenum. The operator will vary his procedure dependent on what part of the intestine is readily visible: (1) The cecum lies either in the epigastrium or right upper quadrant and the proximal half of the colon is visible. (2) The small intestine alone occupies the front of the abdomen and the colon is not easily found. (3) Distention of only the duodenum and stomach indicates that the obstruction is in the lower duodenum. (4) A dilated small intestine and collapsed colon indicates the probability of a stenosis or atresia of the small intestine.

In the first, the duodenum is obstructed by the incompletely rotated cecum. This is due either to direct pressure of the cecum on the duodenum, or caused by peritoneal bands and membranes which extend between the cecum, across the duodenum, to the infrahepatic or upper right gutter areas. When there is an incompletely rotated colon present, one must follow a systematic procedure in order that he not become confused. He must divide the peritoneal membranes between the cecum and right half of the colon to the other structures. This usually exposes the underlying lower half of the duodenum which is now relieved of its obstruction. The right colon must be mobilized by dividing its lateral and superior attachments so that it can be placed in the left side of the abdomen. The duodenum may now be seen in a fetal position, passing downwards on the right side of the superior mesenteric artery. However, it may be acutely kinked at the duodenojejunal junction by other membranes. The peritoneal attachments of the duodenum, with its various bands and including the ligament of Treitz, are then freed so that the distal half of the duodenum is permitted to pass downward and vertically into the jejunum. Sometimes, the mesentery at the root of the artery may be quite indurated and shortened; and it may carry a small vessel. If the end of the duodenum remains dilated and elongated, there may be an obstruction at its lower end. The surgeon must be certain that there is no intrinsic duodenal obstruction coexisting. He may try to massage downwards the intestinal contents, or to explore the lumen with the indwelling gastric tube. Some prefer to insert a small rubber tube through the anterior wall of the stomach and use this to explore the duodenum. It may be left in for postoperative feeding. The duodenum may be obstructed by spasm of its wall, with or without induration. There may be an unrecognized obstructing septum or a perforated diaphragm or mucosal shelf. Gas should be milked down the entire

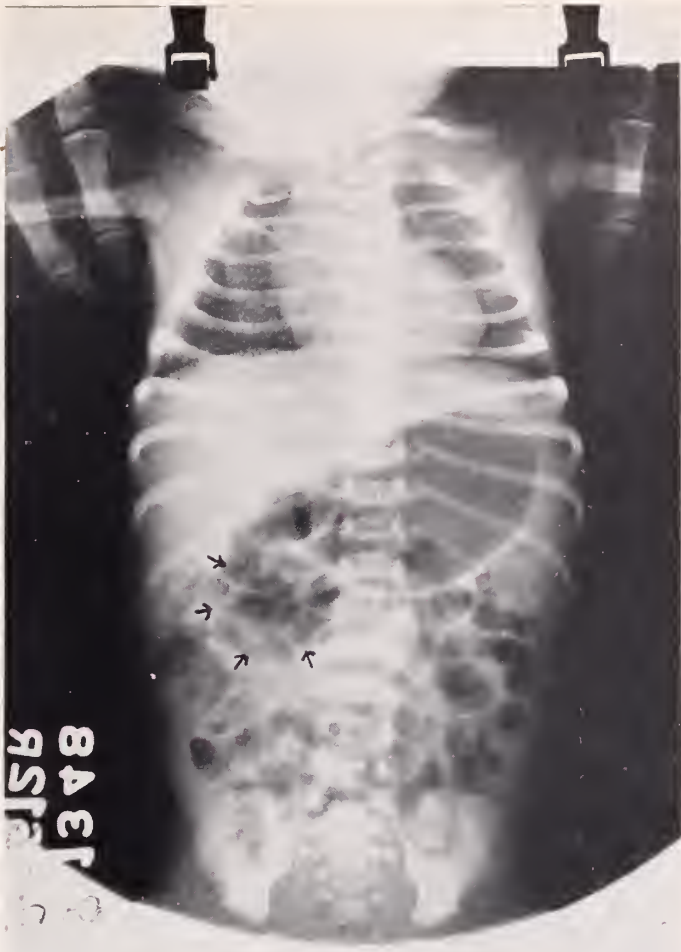


FIG. 3. (a). Two day old newborn who had persistent vomiting of bile-stained fluid. Flat plate of the abdomen shows gaseous distention of the stomach and second part of the duodenum, as indicated by the arrows. Air is also scattered throughout the small and large intestine. While there is colonic gas, absence of air in the right iliac fossa (as would be present in the cecum) indicates the possibility of failure of descent of the cecum and right colon. (b). Gastrointestinal studies reveal distention of the stomach as noted on the flat plate, and definite dilatation of the cap as well as the second part of the duodenum and first portion of the third part of the latter. There is a trough-like deformity noted in this region suggesting extrinsic pressure. A small amount of barium passes the dilated duodenum. (c) 24 hour roentgenogram reveals scattering of the barium throughout the small and large intestine. Patient had almost complete duodenal obstruction due to compressing bands accompanying a malrotated cecum (in the epigastrium). Obstruction was relieved by severing the bands, straightening out the duodenum, and placing the cecum in the lower left side of the abdomen. (Drs. David S. Dann and Sidney Rubin, Roentgenologists.)

intestine to be certain no other obstruction is present. If there is a kink in the intestine due to heavy bands, and the mesentery is indurated and shortened, it may be necessary to do an anastomosis around this point. This is sometimes indicated at the duodenojejunal junction.



After the cecum has been placed in the left side of the abdomen and the duodenal obstruction relieved, these patients thereafter remain free of symptoms. It is not necessary to fix the cecum in the right iliac fossa; although this may be done. To overcome the rotation of the cecum on its longitudinal axis, the following technique may be used (11). An incision is made along the right lateral



FIG. 3 B

border of the small intestine and a similar incision just to the right of the right border of the unrotated colon. The colon is pulled to the right, in the normal adult position, which places its mesentery anterior to the small intestine. An incision is made in the transverse mesocolon and the small intestine is pulled down through it to be placed in its normal position posterior to the transverse mesocolon. The terminal ileum is severed, brought through the opening, and then

the ends are anastomosed together in their definitive position. In order to free the terminal ileum adequately to pull it forward from behind the cecum, it may be necessary to cut some of its mesentery. It may then be a safer procedure to close the open end of the terminal ileum, and do an end-to-side anastomosis of



FIG. 3 C

the proximal end of the terminal ileum to the ascending colon. The results are good following this procedure.

If the colon is found in the unrotated stage, it already occupies the left side of the abdomen, and the small intestines the right side. It is then necessary only to liberate and explore the duodenum as already described. The areas denuded of peritoneum regenerate rapidly in the infant.

When the abdomen is opened and only small intestine is readily visible, one

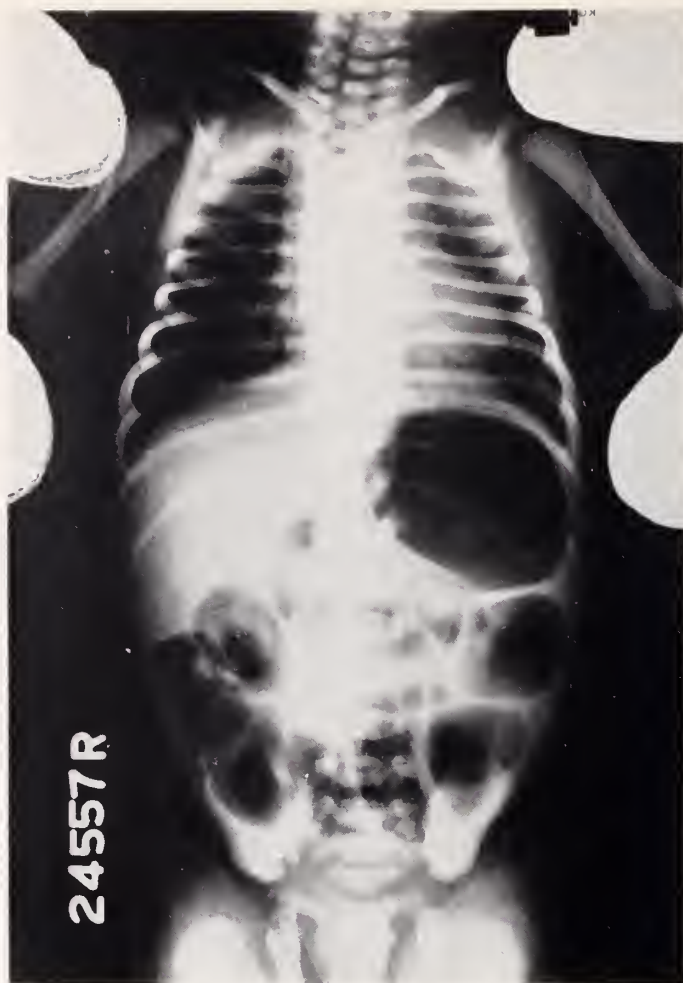


FIG. 4. (a). Three day old newborn, who on the third day of life developed abdominal distention and vomited bile-stained fluid. Plain reontgenograms of the abdomen reveals considerable gaseous distention of the stomach as well as contiguous loops which appear to be duodenum. There is irregular gaseous distribution throughout the intestinal coils. It is difficult to determine where the gas shadows terminate in the duodenum; and which of the shadows belong to large or small bowel. (b) After two days of intermittent vomiting of bile-stained material, the distention subsided. A week later, gastrointestinal studies and enema were performed with thin barium. This reveals an abrupt termination of the duodenum in its third part. Barium enema reveals failure of rotation of the cecum, which lies in the upper right quadrant of the abdomen. The appendix is plainly visible here. The barium enema has demonstrated that the gas shadows seen in the flank in the plain film were due to small intestine and not to the large as one would ordinarily conclude without the advantage of barium enema observations. This patient continued to remain well and free of symptom's three months later. (Drs. David S. Dann and Sidney Rubin, Roentgenologists.)

should suspect that a volvulus of the midgut is present. The intestine may contain only a small amount of gas, or be collapsed. If the twist is tight enough, it will compress the superior mesenteric artery. This may cause a deep bluish

discoloration or gangrene of the intestine. The color may be slightly dusky if the compression is not too marked. To meet this problem without becoming confused, the whole small intestine must be delivered out of the incision onto the warm and moist abdominal pads. Sometimes, it seems some of the coils are herniating through a defect in the mesentery. The volvulus may now be recog-



FIG. 4 B

nized: it usually turns in a clockwise direction and has half to two or more complete twists. It is reduced by correctly untwisting it. When the color returns to the coils, the operation is not complete until the malrotated cecum is taken care of. The cecum and ascending colon occupy the right upper quadrant of the abdomen and may compress the duodenum as described above in uncomplicated malrotation. These compressing membranes must be released. The cecum and



first half of the colon are mobilized and placed in the left side of the abdomen. This is done by incising the bands lateral and superior to the cecum. The duodenum should also be freed to permit it to pass downwards into the jejunum. Failure to proceed beyond the untwisting of the volvulus may permit a mortality due to an unrecognized duodenal obstruction.



FIG. 5. A 55 yr. old man who had recurrent episodes of midabdominal pain, associated with nausea and vomiting. Barium enema reveals the cecum to lie to the right of the midline in the pelvis. All of the colon lies in the left side of the abdomen. This represents a failure of rotation of the cecum. Patient felt well after examination and declined to have further studies.

Intrinsic duodenal obstruction may be present. It is relieved in the following manner: (1) A longitudinal incision is made through the duodenal wall over the obstruction, the diaphragm is excised, the mucosal wound is sutured, the intestinal incision is closed in a transverse line. (2) The intestinal flow may be diverted around the obstruction by a duodenojejunostomy or gastrojejunostomy. The intestinal tube may then be pushed beyond the suture line or anastomosis. If the intestine is quite small distal to the obstruction, the procedure may be assisted by distending this portion with air, saline or sterile mineral oil injected

into the lumen with a small needle. It may be necessary to make a small incision into the lumen to be certain the injected medium enters the lumen and does not dissect along the layers of the wall.

Because of the obstruction and distention, the proximal intestine may have a very thin wall. To protect the suture line, the intestine must be kept deflated, if possible. Some feel the indwelling tube cannot be tolerated by the infant for



FIG. 6. The entire large intestine is filled with barium, including the ileum. The hepatic flexure is down and to the left as compared to the normal position. The cecum is in the upper right quadrant and its fundus is directed upwards and to the right so that the ileocecal valve lies along the right margin of the cecum rather than on its left. The cecum and ileum remain fixed in their positions suggesting a failure of complete rotation and descent of the cecum into the right lower quadrant. This patient does not have intestinal symptoms. (Drs. David S. Dann and Sidney Rubin, Roentgenologists.)

more than a day or so. It might be safer to place two small tubes into the stomach as gastrostomy: one to be passed beyond the anastomosis for feedings, and the other to drain and keep the stomach deflated until the sutures have a chance to heal. Generally speaking, the more proximal the point of atresia or stenosis, the better are the results.

Follow up studies on cases in which the cecum was liberated to lie in the left

side of the abdomen show that they have been free of symptoms. After the reduction of a volvulus, when the other defects have been properly treated, the patients generally remain free of illness and complaints.

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# MELANOMA OF THE SMALL INTESTINE AND STOMACH

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The relative infrequency of tumors of the small intestine is well known; melanomas comprise a small fraction of these tumors. A review of the literature reveals only thirty-one reported cases of melanoma of the small intestine, of which ten are recorded as primary in the intestine and twenty-one as metastatic from melanotic foci elsewhere in the body. In none of these cases was the diagnosis suspected pre-operatively or ante-mortem in those who were not explored surgically.

This report describes two cases of melanoma of the small intestine associated with melanoma of the stomach, which were secondary to primary melanotic lesions in the skin. In one case, the diagnosis was made at the operating table after x-ray studies had indicated the presence of tumor masses in the small intestine and stomach. In the second case, the diagnosis was based on the history of a recently removed pigmented nevus, x-ray findings of multiple lesions in the stomach and intestine, and the discovery of melanin in the urine.

## CASE REPORTS

*Case 1. History:* C. S. C., an Italian born housewife, aged 62 years, was referred to the Surgical Service of Fordham Hospital by Dr. M. M. Levites on December 8th, 1946. She then complained of abdominal pain, vomiting and constipation of two months duration. Before the onset of these symptoms, she enjoyed good health; she had no previous operations. The pain was right-sided, cramp-like and not relieved by bowel movements. The latter were loose and frequent at the onset, and later became increasingly less frequent so that constipation was sometimes present. Her appetite diminished and she lost ten pounds. She vomited occasionally after eating, but no blood was seen in the vomitus. She had not noticed any bloody or tarry stools. For three weeks before admission, she ran a low grade fever to 101°F. which did not respond to sulfonamide therapy.

*Examination.* The patient appeared chronically ill, pale and anxious. The significant findings were limited to the abdomen, where fulness and moderate deep tenderness were encountered in the right lower quadrant. A small umbilical hernia could be easily reduced. On rectal examination, a firm fixed mass, 5 cm. in diameter could be felt through the anterior wall. Sigmoidoscopy disclosed no evidence of an intrinsic lesion for 25 cm.

*Laboratory Data.* Stool examination disclosed a strongly positive guaiac reaction. No ova or parasites were seen. The hemoglobin was 6.0 Gm.; red blood cells, 2,650,000; white cells, 12,150 with 66% polymorphonuclear leukocytes; platelets, 230,000. Blood sugar was 142 mg. percent, urea nitrogen, 12 mg. percent. Icterus index was 8, prothrombin time, 16 seconds (control 18 seconds).

Barium enema examination revealed no abnormality. Barium meal examination revealed a large, ovoid, smooth filling defect, measuring 6.5 cm. in length in the stomach, which arose from the greater curvature aspect. The mucosal folds in this region appeared to be displaced and compressed. The appearance was that of an intraluminal gastric mass. In addition, there was a large, irregular mass measuring about 9 cm. in length in the right

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lower quadrant apparently within a loop of distal ileum. The ileal mass was surrounded by a thin, irregular stream of barium (figs. 1, 2).

*Course.* A provisional diagnosis of lymphosarcoma or Hodgkin's disease of the stomach and small bowel was made.

At operation on December 30th, 1946, the stomach was found to contain a mass, 7 cm. in diameter, occupying the middle third of the greater curvature. This mass seemed to shine through the serosa with a dark, bluish hue. Eighteen inches from the ileocecal valve, the ileum was markedly distended and contained several polypoid spongy masses varying



FIG. 1. *Case 1.* Filling defect on greater curvature aspect of stomach indicative of intraluminal mass.

in size from 2 to 8 cm. in diameter. The same dark bluish color seen in the stomach was visible in these masses. The terminal ileum was resected for a distance of two feet and an end to end anastomosis performed near the ileocecal valve. The diagnosis of malignant melanoma seemed to be obvious on gross examination, and since the patient's condition was not satisfactory at this point, it was deemed advisable not to carry out any gastric resection. The mesentery was full of numerous black masses varying in size from 0.5 to 3 cm. The liver was not involved. Post-operatively, the patient did not do well. Persistent fever, diarrhea, and drowsiness were unaffected by therapy. On January 9th, 1947, a mild convulsion occurred, lasting two minutes, accompanied by twitching and tremors of the

right arm and left leg. This was repeated on several succeeding days and was followed by a period of disorientation and hallucinations. Coma supervened and death resulted on January 19th, twenty days after the operation.

*Pathological Report*—(Dr. L. Millman)—Grossly, (fig. 3), the specimen was a 22 inch portion of dilated small bowel with a 4 inch wide portion of mesentery. Within the lumen, three large firm cauliflower, reddish black tumors were seen, each approximately 7 cm. in diameter, firm in consistency. Although the large masses appeared to occlude the lumen, a semicircular narrow passageway still allowed soft feces to pass.



FIG. 2. Case 1. Large irregular mass within a loop of distal ileum

On cut section, the exposed surface presented a brownish black pigmented tissue, attached to the inner wall of the gut by a broad gray white fibrous pedicle. The degree of pigmentation of the tumors varied.

*Histological examination* (fig. 4) revealed an extremely cellular anaplastic tumor divided into irregular sized lobules by fibrous septa. The cells occurred in compact sheets and assumed a polygonal shape, although, in some areas, compression effects were noted, with distortion of the cellular outline. The nuclei were prominent and possessed abundant stippled chromatin and nucleoli. In the cytoplasm, dark brown pigment granules were noted, typical of melanin deposits. Scattered areas of hemorrhage and necrosis were seen. In one of the sections taken through the wall of the small intestine, the tumor was re-



FIG. 3. *Case 1.* Resected ileum containing three large cauliflower reddish black masses

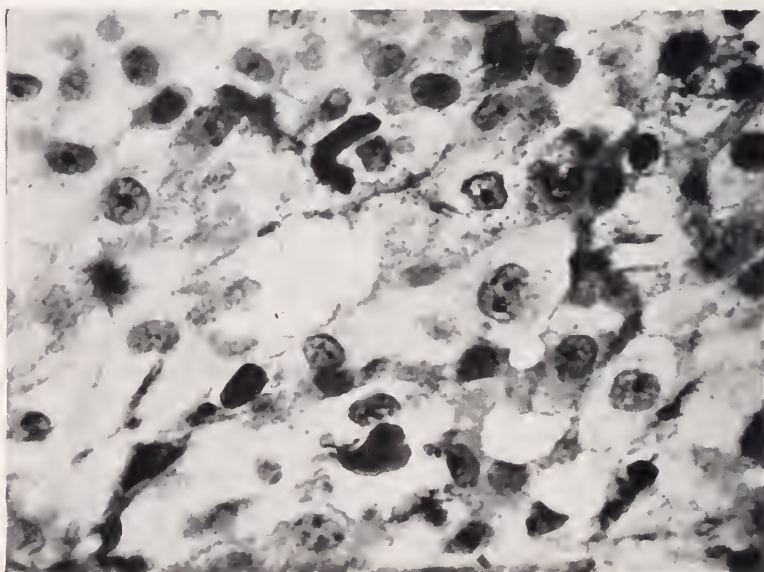


FIG. 4. *Case 1.* Histologic section of one of the masses showing melanin deposits

placing both the mucosa and submucosa, but was not infiltrating the muscularis. In typical areas, the melanin cells were loaded with dark brown pigment granules. The mesenteric lymph node was infiltrated and was almost entirely replaced by melanin cells.

These studies confirmed the diagnosis the malignant melanoma made at operation.

*Comment.* Immediately after the operation, a search was instituted for a primary melanotic focus. On the skin of the back at the level of, and slightly to the left of the mid-dorsal spine, a small crescentic lesion about the size of a dime was found. It was slightly raised



FIG. 5. *Case 2.* Mass situated within the body of the stomach on the lesser curvature and posterior wall.

and contained a brownish blue pigment. Urine examination revealed melanin. The ophthalmologist reported no evidence of melanoma in either eye.

A member of the family stated that three months before the onset of her illness, the patient complained that a birthmark on her back had become swollen and painful after a hot bath. She went to an unlicensed practitioner who tied a string around the birthmark, and the birthmark fell off a few days later.

In the light of the supplementary history and the finding of melanotic spread in the stomach and small intestine, it was felt that we were dealing with a metastatic melanoma secondary to a melanoma of the back.

*Case 2. History:* E. R., a German born housewife, aged 44 years was admitted to the



Mount Sinai Hospital under the care of Dr. H. Nathan on November 20th, 1944, complaining of nausea, vomiting, abdominal pain, constipation, diarrhea and weight loss for five weeks. Her past history included a cholecystectomy for stones in 1932 and a hysterectomy for fibroids in 1943. In 1942, an irritated pigmented mole was excised from the back of the neck. In October 1944, a mass was removed from the right groin, which on pathological examination, was reported as melanoma.

*Examination.* The patient appeared acutely ill. There was a healed scar on the back of the neck. A node, 4 cm. in diameter was felt in the right groin. Signs of incomplete intesti-



FIG. 6. *Case 2.* Numerous circular filling defects scattered throughout the jejunum and ileum.

nal obstruction were evident with abdominal distention and some tenderness in both flanks. These subsided in a few days and x-ray examination of the gastro-intestinal tract was undertaken. This revealed a nodule on the lesser curvature and posterior wall of the stomach, (fig. 5) and numerous circular filling defects scattered throughout the duodenal bulb, the jejunum and the ileum (fig. 6). X-ray of the chest showed a metastatic lesion in the right lower lobe. Urine examination revealed melanin.

*Course.* These findings in association with the history of the irritated mole and the right inguinal melanomatous mass, served to verify the diagnosis of melanomatous involvement of the gastro-intestinal tract.

Because of the patient's poor condition, operation could not be done. There was clinical evidence of metastasis to the brain, as shown by twitching, convulsions and mental deterioration. Death occurred on December 21st, 1944. Permission for postmortem examination was not obtained.

#### DISCUSSION

In the thirty-one previously reported cases of intestinal melanoma, the lesion was described as primary in ten instances (1-9), and as secondary in twenty-one (10-22). In each of the first group, the basis for this categorization, was that no primary focus was discovered elsewhere in the body, despite careful search. In the twenty-three cases of secondary melanoma, a primary lesion was discovered either in the skin or the eye. In six cases, melanoma was found in the stomach (2, 14, 17, 18, 22), in addition to lesions in the small intestines. Our cases can be classified as secondary melanomas and presented both gastric and intestinal involvement.

It is hardly likely that these thirty-three cases are indicative of the total number of instances of melanomatous involvement of the gastrointestinal tract. The tendency of melanoma to metastasize widely is well known, and no organ of the body is exempt. It is probable that melanoma of the gastro-intestinal tract is more common than these reports would indicate. Complete descriptions of all cases are not available since some of these were reported in journals of pathology without reference to clinical details. In those histories in which clinical information was provided, it is noteworthy that nine out of ten primary intestinal melanomas were found in men, only one in a woman. The age distribution was from 35 to 67. All cases occurred in members of the white race. The diagnosis was not established pre-operatively or ante-mortem in any of these. Only one of the primary cases presented co-existing melanoma of the stomach (2).

In the twenty-three secondary cases, information as to age, sex, and clinical course was not fully given. In those cases where such details were provided, the sex distribution was heavily weighted toward the male, 13 men and 3 women being the victims of melanoma of the intestinal tract. All of these cases involved individuals of the white race. The age distribution was from 33 to 50. No mention of pre-operative or ante-mortem diagnosis is made in any of these reports. Five of the patients displayed simultaneous melanomatous disease of the stomach and small intestine (14, 17, 18, 22).

A review of the clinical course in all patients indicates that the abdominal symptoms were not distinctive. Signs of incomplete intestinal obstruction, such as nausea, vomiting, abdominal distention, constipation alternating with diarrhea and flatulence were common to all. Ultimately, all patients displayed signs of generalized metastasis.

Intussusception occurred in twelve cases (1, 3, 6, 7, 8, 12, 14, 19, 20, 22). In seven patients, this developed early enough in the course of the disease to permit operation (1, 3, 6, 7, 8) for relief of obstruction. Four (1, 3, 6, 8) died shortly after surgery and the others were alive (12, 21) at the time of writing.

Since all of the lesions, whether discovered at operation or at autopsy, are described as tumor masses projecting from the mucosa into the lumen of the bowel, it is not difficult to account for the intussusception.

Roentgenographic findings are described in nine cases. In one case (2), studies disclosed evidence of gastric retention and grouping of the intestines in the mid-line, as though by adhesions. In a second case (3), barium meal examination revealed evidence of small bowel obstruction with a filling defect in the cecum and proximal descending colon. At operation, an intussusception one and one-half feet long was found due to a tumor in the terminal ileum. The colon was free of disease. In a third case (5), x-ray studies disclosed an uneven defect at the base of the duodenal cap with persistent raggedness of the pylorus suggesting an infiltrative pathologic process. At operation, multiple melanotic tumors of the intestine were seen, but no abnormality was found in the stomach or duodenum.

In the fourth case (7), barium studies were not done because the patient entered the hospital in acute intestinal obstruction. Scout film of the abdomen revealed a stepladder pattern characteristic of small bowel obstruction. At operation, sixteen tumor masses were found in the small intestine, several of which were contained in an ileocecal intussusception. The fifth case (8) disclosed evidence of pyloric obstruction on barium meal study and no sign of intestinal disease. At operation, the stomach was uninvolved, and a jejunal intussusception due to a tumor was resected. The sixth case revealed a constant irregularity in the upper half of the descending duodenum which represented a melanomatous invasion of the second and third parts of the duodenum, as seen at operation and at autopsy (13).

The seventh case (14), on x-ray study, revealed a polyp of the stomach, a finding which was later verified at autopsy. At operation, the stomach apparently was not explored for possible polyp, but multiple melanomas were seen in the small intestine and an intussusception of the lower ileum was removed. The eighth case (20) in which an intussusception of the ileum was found at autopsy, had negative findings at the time roentgenologic examination was done. The ninth case (21) presented "a distinct abnormality involving one of the jejunal loops which showed a distention of its lumen and a distortion of its mucosal pattern. Fluoroscopically, an area of constriction was observed at the end of the distended loop but this could not be demonstrated on the films. No delay in passage through the stomach and small bowel was noted".

With the possible exception of the ninth case, none of these cases presented radiographic findings which might have aided in a definitive diagnosis. This may account for the little attention given to intestinal melanoma in textbooks of radiology. The radiographic appearance of intestinal melanoma, as shown by the two cases herewith reported, is that of multiple intraluminal masses with distortion and effacement of the mucosal pattern. A similar appearance may be found in malignant lymphoblastoma and in primary carcinoma of the intestine. However, the association of this radiographic picture with malignant melanoma of the skin or eye is certainly suggestive.

Some difference of opinion exists as to the possibility of primary melanoma of the gastro-intestinal tract. The two patients described in this report had pigmented skin lesions which had been irritated some time before the onset of intestinal symptoms, in one case three months and in the other, two years. Both patients showed signs of generalized metastasis in the later course of their disease. It is a reasonable assumption, therefore, that the intestinal lesions were metastatic.

The location of intestinal melanoma is the same in those cases in which a primary focus was found elsewhere in the body, as in those cases in which the tumor has been assumed to have originated in the intestine. In those cases which have been classified as primary intestinal melanomas, the only basis for the conclusion that the lesions arose in the bowel is the failure to find a source elsewhere.

The case against the primary origin of gastro-intestinal melanoma has been well presented by Herbut and Manges (22) who cite five instances in their own records of intestinal melanoma with melanotic lesions in the skin. They quote Laidlaw (23) who has shown that melanoblasts are found only in the skin and mucous membranes of ectodermal origin. Primary malignant melanomas have been reported in the conjunctiva, optic nerve, breast, vulva, clitoris, uterus, vagina, maxilla, urethra, peripheral nerves, hard palate and anus. Melanoblasts are not present in the stomach or in the small intestine or in the large intestine above the muco-cutaneous junction of the anal canal, as witness the negative dopa reaction in these areas. It is very often possible to overlook certain areas of the skin, especially the lumbar and sacral regions where melanoblasts may be present in the corium. Melanomas of the eye may not be discovered for lack of complete eye examination, both during life and at the autopsy table.

The occurrence of melanoma in other organs after the removal of a skin nevus or an orbital pigmented lesion is well authenticated and is illustrated by the second case in this report. The history of the primary lesion is often forgotten by the patient or not elicited by the physician.

#### SUMMARY

Two cases of melanoma of the small intestine and stomach are described in which the primary focus was in a skin nevus that had been traumatized or operated upon. They are presented to support the concept that gastro-intestinal melanoma is a metastatic growth.

Thirty-one previously reported cases are reviewed with attention to history, symptomatology and radiographic findings. It is suggested that radiographic findings of intra-luminal masses in the gastro-intestinal tract, symptoms of incomplete intestinal obstruction and a history of an irritated skin nevus are characteristic of gastro-intestinal melanoma.

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## MUCOSAL AEROGRAPHIC STUDIES OF THE STOMACH AND SMALL BOWEL

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During the past decade, there has been a slow but steady improvement in the Roentgen diagnosis of gastro-intestinal disease. I well remember when I first started about thirty years ago, the patient swallowed two large glasses of barium mixed with Zulack. Although we fluoroscoped the patient while drinking the mixture, no films were taken until the entire amount had been swallowed. The only view we had of the partially filled stomach was a fleeting one during the fluoroscopic examination. Those were the days of glass plates and gas tubes. We diagnosed inoperable carcinoma; an ulcer situated on the lesser curvature; and had fair results in duodenal ulcers. Most of the wall of the stomach was completely obscured by the barium by the time plates were taken.

The first big improvement was the work of A. A. Berg and his workers who introduced the mucosal method for studying gastric rugae. In this examination, barium sulphate was mixed with warm water until a creamy consistency was obtained; then one or two teaspoonfuls of this mixture were used. The patient was then fluoroscoped and films were taken with the patient in the prone and erect postures. About this time the use of compression devices as well as mechanisms for spot films were also introduced. Ulcers now could be picked up on both the anterior and posterior wall, and the scarring about the ulcers could be demonstrated by the distortion of the rugal pattern. Small tumor masses could also be demonstrated. This method, however, studies only the collapsed stomach and many lesions are better demonstrated by the distended stomach. When the stomach, however, was distended with the barium mixture, many lesions were obscured.

In order to distend the stomach without obscuring it, it is necessary to distend the stomach by air or some other gas. One method was by introducing a Levine tube through the nose down to the stomach and pumping air with a Politzer bag or syringe directly under fluoroscopic control. We have tried this method and found it satisfactory, but rather trying to the patient and time consuming.

Another method to distend the stomach by gas was by giving the patient a Seidlitz powder. While some very satisfactory films were obtained by this method, it was rather difficult to control the amount of gas introduced into the stomach. A great deal of the gas was lost while mixing before the patient drank the fluid.

In the study of the small bowel, the most commonly accepted method was giving the patient the regular barium meal and taking films at hourly intervals. This usually meant that the patient would be in the department or office most of the morning and necessitated considerable work. Shatzki suggested the use of the barium small bowel enema. In this method, a Levine tube was passed through



FIG. 1. MUCOSAL film for study of gastric rugae.



FIG. 2. Normal stomach after administration of club soda showing gaseous distension of stomach.

the nose, down the oesophagus and through the pylorus. A thin barium mixture was then introduced by gravity until the entire small bowel was outlined. On numerous occasions we have used this method and found that while it gave satisfactory results, it was troublesome to the patient. It was also time consuming.

Last year at a meeting of the New York Roentgen Ray Society, Drs. Sidney



FIG. 3. Gaseous distension of stomach with patient in marked Trendelenburg position

Weintraub and Robert Williams advocated the use of iced saline water after administering three ounces of the barium mixture. The hypermotility thus induced gave rapid filling of the small bowel so that the jejunum and ileum were often filled on the half hour film. This method was most satisfactory of all, and I am using it almost as routine with small bowel studies.

The question then arose if these different methods could be combined in one simple routine procedure, and I have devised the following plan.



Three ounces of a mucosal mixture is made by mixing barium sulphate and warm water to a smooth even consistency. It is very important that the mixture be just right. If it is too heavy, that is, if it can be heaped upon a spoon, it will not coat the mucosa freely. If it is too thin, it will pass too rapidly out of the stomach. It should be of a consistency of unwhipped heavy cream. The patient



FIG. 4. Gaseous distension of stomach, patient in Trendelenburg position, demonstrating pre-pyloric ulcer.

has two level teaspoonsful of this mixture and lies on his right side. When the stomach is coated as determined under the fluoroscope, spot films are taken of the posterior and then the anterior wall. The patient then receives a third teaspoonful which is swallowed under fluoroscopic control, and a film taken of the lower end of the oesophagus and the cardiac portion of the stomach. After this, the patient is placed in the erect position, and at least two films are taken. The patient then

takes the balance of the mucosal mixture and another set of films is taken and if the duodenal bulb is at all irregular, polygrams are taken of this or any other suspicious area. We have now completed the first part of the examination, which, in my opinion is very well suited to diagnose gastric and duodenal ulcers. In many patients in which a duodenal ulcer is demonstrated, the gastric examination may end at this time.

It is desirable to distend the stomach without obscuring it by introducing some gas. In order to study the small bowel, the patient should receive iced water. It



FIG. 5. Gaseous distension of the stomach, patient erect, outlining neoplasm of cardia

seemed to me that both of these objectives could be best obtained by giving the patient a small bottle of iced cold club soda. For this I use the individual small bottles of club soda which are kept on ice and are uncapped just before use. Instead of using a glass in which method a large amount of gas is lost when poured into the glass, the patient drinks the contents through a straw or glass tube. In this way there is very little loss of the gaseous content. After the patient has taken about four ounces of the fluid, he is fluoroscoped, and if the distension is not sufficient, he drinks the balance under fluoroscopic control. The patient must be carefully instructed not to belch.

Films are now taken in the erect position, postero-anteriorly and laterally.

The patient is then placed on the horizontal tilting fluoroscope, and preferably under fluoroscopic control the patient is positioned so that the body and antral portions of the stomach are distended. Films now should be taken in this position both antero-posteriorly and postero-anteriorly, and some in the Trendelenburg



FIG. 6. Gaseous distension of stomach, patient erect, demonstrating true gastric hernia with barium in oesophagus beside hernial sac.

position. After these films are taken, the patient is allowed to belch. The gastric examination is now completed. For the study of the small bowel, films are taken until the caecum is reached, which will usually occur in about one hour.

I have outlined a simple technique which really comprises four different examinations.

1. We obtain mucosal films outlining the oesophagus, stomach and duodenum.
2. We obtain a partial filling with a three ounce mixture which is excellent for studies of the gastric mucosa as well as for the diagnosis of the duodenal bulb including polygraphs. The amount of barium, however, is not so great that tumor lesions are obscured.
3. A study of the gaseous distended stomach is also obtained.
4. We also obtain a small bowel study which is usually completed within one hour.

This simple procedure, which consists only of three ounces of barium mixture and a small bottle of iced club soda combines all the benefits of the Berg mucosal technique, the Seidlitz powder and the ice-water hypermotility method.

#### DISADVANTAGES

1. Cooperation of the patient is necessary, otherwise the distension is not satisfactory. Cooperation may be impossible either because of illness of the patient or stupidity.
2. Gastric motility is not accurately determined because of the induced hypermotility. This is not as important as it seems, as any trained roentgenologist can recognize delayed motility while examining the patient with the three ounce mixture, but no definite standard can be set.
3. I do not think it should be used if there has been any recent bleeding and an ulcer pocket is demonstrated with the three ounce mixture. In these cases, I do not give the club soda, but give another glass of the barium mixture and take a film at four hours to determine gastric motility. The procedure should not always be fixed, but should be varied for the individual case.

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## THE RELATION OF NEUROCIRCULATORY ASTHENIA TO ANXIETY NEUROSIS

B. S. OPPENHEIMER, M.D. AND MENARD M. GERTLER, M.D.

Neurocirculatory asthenia is an ancient disorder, but was first clearly defined by DaCosta in his vivid clinical description of the "irritable heart of soldiers" observed during our own Civil War. This he published in 1871 (2). The same condition was also very disabling during World War I, and was given the name of the "Effort Syndrome" by Sir Thomas Lewis (8). The experience of one of us was based, at first, on observing extreme cases of this condition at Colchester under Lewis in 1917, and subsequently on seeing milder instances in the American Army and in civilian and hospital practice. Lewis' designation, the "Effort Syndrome" was based on the resemblance of the symptoms and signs to those resulting in normal people after marked physical effort (8). The six American medical officers at Colchester were not quite in sympathy with this new name, and in 1917 the term neurocirculatory asthenia was suggested by one of us (B.S.O.) (9). This name was purely descriptive and did not include the word *cardiac* or *heart*; so that it was readily accepted for the diagnosis of men in the service, for disability, for drafting, and for civilian practice. In addition there are some 38 other names for the same or a similar disorder. It occurs in an acute and in a chronic form; that which follows refers largely to the chronic form.

In 1944 White, Cobb, Chapman, Cohen and Badal (10) published new and interesting "observations on neurocirculatory asthenia". They wrote: "The condition long recognized by the neuropsychiatrists as resembling in some of its manifestations our chronic cases of neurocirculatory asthenia, though not really synonymous, is the anxiety neurosis." The resemblance of the two conditions was emphasized by Dr. A. E. Cohn in 1919 (1).

This fall, Dr. Mandel E. Cohen wrote one of us (B.S.O.) a letter on this subject of the relation of neurocirculatory asthenia to anxiety neurosis, and posed what appeared to be 4 simple questions:—

- "1. In your opinion, what are the symptoms of anxiety neurosis?
2. What symptoms of anxiety neurosis do not occur in neurocirculatory asthenia?
3. What symptoms of neurocirculatory asthenia do not occur in anxiety neurosis?
4. If you personally examined a group of patients who had been diagnosed 'anxiety neurosis', based on symptomatology, how would such patients differ from patients with neurocirculatory asthenia?"

In his letter of November 14, 1949, he "wondered if a good deal of the discussion in this field of anxiety neurosis and neurocirculatory asthenia is not a discussion of the use of terms which have never been defined." These questions prompted us to review the concepts of neurocirculatory asthenia and anxiety neurosis, and to attempt to define these terms.

By the usually accepted definition, neurocirculatory asthenia is a clinical syn-

drome, not a disease *sui generis*, characterized by dyspnoea, palpitation, precordial pain, fatigability, nervousness, dizziness, headache, and a great variety of associated symptoms and signs called forth or enhanced by effort, and in which no evidence of structural disease can be found to which the symptoms may be related. If an organic disease, such as pulmonary tuberculosis, Graves' disease, brucellosis or mitral stenosis is proven and accounts for the symptoms, we prefer to classify the disorder primarily under that term with or without a superimposed neurocirculatory asthenia.

It has been somewhat difficult to give a single definition of anxiety neurosis which would be acceptable to all. In general there are two views. The clinical psychiatrist would probably agree with the following definition which is suggested. Anxiety neurosis is a psychic disorder in which the predominant symptom, descriptively speaking, is a feeling of *irrational* anxiety and fear, or their equivalent, associated with a great variety of other symptoms and signs referable to different organ systems, such as the cardiovascular, respiratory, genito-urinary, gastro-intestinal, dermatologic, etc. (7). This definition is a phenomenological one. There is a second aspect of the definition however, which takes into account (a) the etiology and (b) the psychopathogenesis. For this formulation we are greatly indebted to Dr. Sydney G. Margolin. From the psychoanalytic point of view, anxiety in the sense of irrational fear is a psychophysiological alarm reaction to the fact that a given impulse may break through and be expressed in the form of some unacceptable erotic or destructive action alien to the personality. Ordinarily these unacceptable manifestations of impulses are held in check by those parts of the personality known as character traits or the so-called conscience,—so that a direct expression of these impulses does not reach awareness. If for any reason a character trait or the conscience apparatus decompensates, then the impulse is unchecked, threatens to reach awareness, and the alarm reaction, i.e. irrational anxiety, results. This response should be differentiated from the situation in which the danger stimuli are realistically apprehended.

The difficulty in comprehending an operational definition of anxiety neurosis as given by psychiatrists is due to differences in the systematizations of human psychology held by various schools of psychiatry. In any event, a degree of psychiatric training and experience on the part of the reader is apparently required.

Having defined both neurocirculatory asthenia and anxiety neurosis, one is immediately impressed with the great similarity of symptoms. How then may one distinguish between the two syndromes? In order to make a satisfactory comparison of the two clinical syndromes, anxiety neurosis and neurocirculatory asthenia, the frequency occurrence of several symptoms was ascertained in a group of (a) 74 patients with neurocirculatory asthenia taken from the private records of one of us (B.S.O.) and (b) 50 patients with anxiety neurosis selected from the consultation service of The Mount Sinai Hospital, New York, through the courtesy of Dr. Herman Lande. The symptomatology of the two groups of patients was compared with each other and with a group of 149 normal indi-

viduals (140 men and 9 women). It will be observed in Table I, that (a) all the symptoms selected are virtually absent in the control group; (b) in neurocirculatory asthenia there is a significant preponderance of palpitation, precordial pain, chest pain, total chest pain, dyspnoea and fatigability; (c) in anxiety neurosis, there is a significant preponderance of nervousness, headache, nausea and anorexia. These observations are not new, for they are consonant qualitatively and differ slightly quantitatively from the reports by White *et al* (10) and Wheeler *et al* (11).

TABLE I  
*Comparison of symptoms\* in anxiety neurosis, neurocirculatory  
asthenia and putatively normal individuals*

	ANXIETY NEUROSIS (%)		NEUROCIRCULATORY ASTHENIA (%)		NORMALS (%)
	P†	T†	P	T	
Palpitation	22	44	82	92	6
Total Chest Pain‡	26	28	72	88	8
Dyspnoea	31	48	70	84	5
Nervousness	54	80	42	66	14
Dizziness	40	52	53	64	8
Fatigability	20	22	60	62	7
Precordial Pain	20	22	48	60	2
Headache	66	82	34	42	12
Paresthesia	18	26	28	38	1
Sweating	12	18	12	32	9
Weakness	18	20	24	32	2
Chest Pain	6	6	24	28	6
Insomnia	2	2	8	18	2
Syneope	6	9	11	14	6
Belching	8	20	8	12	6
Pollakiuria	0	6	1	3	2
"Heart Burn"	8	14	1	3	12
Anorexia	4	12	0	2	1
Nausea	10	38	0	2	1
Abdominal Cramps	10	16	0	1	1

\* Symptoms are listed as per cent of total cases.

† P—presenting symptom.

‡ T—total symptoms (presenting and also elicited by inquiry).

I—on inquiry.

‡The term total chest pain includes precordial pain and other chest pain. Chest pain is any pain referable to the chest which is not localized in the precordial area.

While there is no complete dichotomy of symptomatology between neurocirculatory asthenia and anxiety neurosis, there are sufficient degrees of separation of the various symptoms to warrant making a distinction between the two syndromes. The symptomatology of neurocirculatory asthenia is mainly referable to the cardiorespiratory system while the symptomatology in anxiety neurosis encompasses several systems without being specifically related to any one (see fig. 1).

## DISCUSSION

"In 1894 Freud (3) described the clinical symptomatology of anxiety neurosis under the following headings: general irritability, anxious expectation, the anxiety attack proper, rudimentary anxiety attacks (for example, disturbances of the heart's action, disorders of respiration, sweating, tremors, ravenous hunger, vertigo, vasomotor neurasthenia, paraesthesias), *pavor nocturnus* of adults, certain phobias, 'the first relating to common physiological dangers, the others to locomotion'." This is a phenomenological description of anxiety which is as true to-day as it was in 1894. The psychologic interpretation of it, however, is very different now from what it was then. Freud's earlier view (before 1926) was that the impulse was blocked and then converted into anxiety. The definition previously expressed by Dr. Margolin is based on the change made by Freud (4) himself as expressed in 1926 in his volume entitled "Hemmung, Symptome und Angst". This is the current view and seems to have stood the test of further experience.

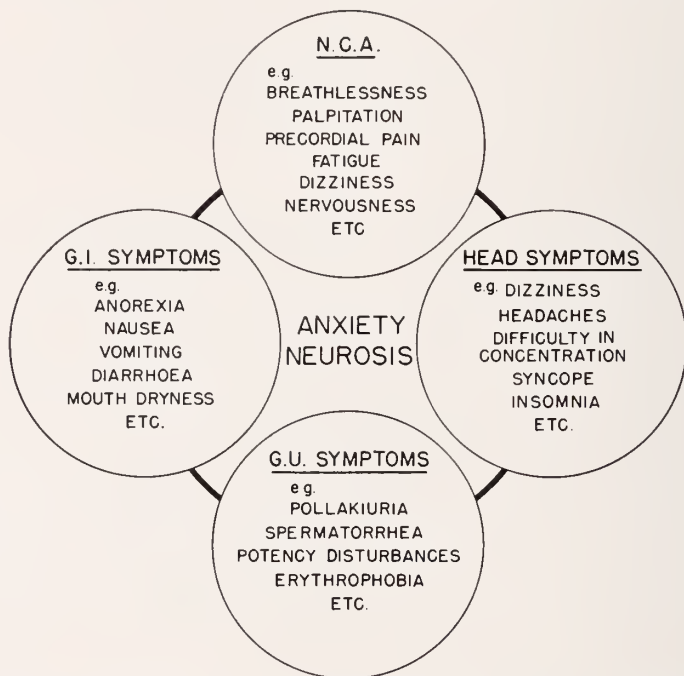
According to all this, anxiety neurosis is a very broad term; the condition is very widespread, and some of the clinical symptoms may be common to the different variants of anxiety neurosis. Owing to the individual psychological make-up, different organs or organ systems are selected for the manifestations of the major symptoms. One may speak of psychologically-charged organ choice. So there are subdivisions of anxiety neurosis based on the presenting major symptoms; or one may consider anxiety neurosis the parent syndrome, and the variants as the offspring of that parent. There may be a pure uncomplicated form of anxiety neurosis without organ involvement, but in general medical practice it must be rare. The idea of a general anxiety neurosis with variants is depicted in the diagram (fig. 1). Of course there is considerable overlapping in the symptomatology of these subgroups based on organs or organ systems of reference. It is convenient to speak of uncomplicated anxiety neurosis, of neurocirculatory asthenia, of anxiety neurosis with predominantly gastrointestinal symptoms, or with head symptoms, genito-urinary symptoms, or even dermatologic symptoms.<sup>1</sup>

There are practical and sound reasons for retaining the name "Neurocirculatory Asthenia". The cryptic "Neurocirculatory Asthenia" is accepted in the official nomenclatures, and by civilian physicians and at least the cardiologists know what is meant by the term. The term neurocirculatory asthenia is particularly useful for military purposes, as the registrant, draftee or soldier does not get the implication that he has an organic heart condition. It gives the name to a syndrome with distressing symptoms such as precordial pain, which if called cardiac, might incapacitate the sufferer for any real work or service. It seems wise to continue this term for use by the physician. In addition every patient suspected of having neurocirculatory asthenia should have an independent psychiatric examination. The term used to designate the condition may be of great practical importance in the success or failure of management. Thus in World

<sup>1</sup> Neurodermatitis and certain instances of pruritus ani and of urticaria belong to this group.



War II, the term "Exhaustion", obviously a euphemism, was officially adopted for labelling all psychiatric casualties in the forward areas of the theater of war (6). When the tag was read by the soldier it obviously indicated to him a temporary and a recoverable condition. Incidentally, it may be recalled that in 1917-18 at Cochester an effort was made by a psychoanalyst to treat the "Tom-mies" invalided from France for neurocirculatory asthenia. Unfortunately at that time there were no satisfactory results with this type of psychotherapy, but all the conditions and the attitude of the invalided soldiers were very unfavorable to success. Recently however with contemporary psychoanalytic and other



MAJOR SYMPTOMS IN SUBDIVISIONS OF ANXIETY NEUROSIS

FIG. 1

psychotherapeutic methods more promising results have been obtained by competent psychiatrists and psychoanalysts.

It is said that at present in the Veterans Hospital a patient with neurocirculatory asthenia has the benefit of an expert psychiatric study and also that he is classified as to the grade of disability and compensation independently by a cardiologist and by a psychiatrist. He may receive double compensation for his neurocirculatory asthenia status and for his psychoneurotic disability. One thing is now clear that giving pensions or stopping the precipitating cause of the neurocirculatory asthenia, as for example by separation from the Army or cessation of war, does not necessarily bring partial or complete relief of the symptoms. In Grant's (5) follow-up of 601 neurocirculatory asthenia patients observed five years after discharge from the British Army, only 15.3% were fit, 17.8%

were improved, 56.2% were stationary and 3.2% were worse. Wheeler (11) *et al* reported that in a series of 173 patients diagnosed twenty years earlier as neurocirculatory asthenia, 12% have recovered fully, 35% have symptoms but no disability, 38% have symptoms with mild disability and 15% have symptoms with moderate or severe disability. Wheeler *et al* also concluded that neurocirculatory asthenia certainly does not lead to a high mortality rate. (It may be mentioned that no post-mortem report on a case of neurocirculatory asthenia has been found in the literature.)

#### SUMMARY

The long-standing question of the relation of neurocirculatory asthenia to anxiety neurosis may be best answered at the present time, by considering the former as a variant of the latter. One may consider anxiety neurosis as the general term with variants depending upon the predominant presenting symptoms; thus neurocirculatory asthenia is a variant in which the symptoms are referred to the cardiovascular, respiratory and nervous systems. There are other variants in which the presenting symptoms are referred to other organs or organ systems, such as the gastro-intestinal, genito-urinary, etc. The symptoms in all these groups overlap.

The term neurocirculatory asthenia ("N. C. A.") should be retained as it has certain advantages over the many other names suggested. It is accepted in the official nomenclatures and is generally used by medical officers, physicians of the Veterans Administration, civilian physicians, cardiologists and by some neuropsychiatrists. It is non-committal and has no connotation which may do harm to the soldier so afflicted.

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# THE PSYCHOSOMATIC APPROACH TO NEUROCIRCULATORY ASTHENIA

## A SUPPLEMENT TO THE RELATION OF NEUROCIRCULATORY ASTHENIA TO ANXIETY NEUROSIS

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It should be emphasized that the syndrome which in 1917 (1) was named "neurocirculatory asthenia" by Dr. Oppenheimer was originally observed in military combat situations. Anxiety neurosis, on the other hand, is a syndrome that was defined in a civilian environment (2). With the establishment of these two terms in nosological practice to cover a relatively unclassified group of somatic and psychic symptoms, anxiety neurosis and neurocirculatory asthenia began to appear as diagnoses in both civilian and military settings. It is important to realize that neurocirculatory asthenia as a term stresses the pathophysiological manifestations, whereas anxiety neurosis calls attention to the psychopathological phenomena. The significance of this distinction becomes apparent when the psychiatrist diagnoses anxiety neurosis in a patient who, according to the internist, exhibits neurocirculatory asthenia. In addition, this difference may be expressed by the patient's choice of his presenting symptom which may be psychological or physical. In fact this unconscious selection may determine whether the patient will be referred to the psychiatrist or to the internist.

This illustrates most pointedly the futility of a dualistic approach in the theory and practice of medicine, i.e., the failure to view mental activity as a biological process. The same disease can be recognized as two different entities according to the orientation, or, should one say, the prejudices of the observer? Dr. Oppenheimer, in collaboration with the late Dr. Rothschild, wrote a paper in 1918 (3) on this subject. Its title is illuminating—"The Psychoneurotic Factor in the Irritable Heart of Soldiers". This notable pioneer contribution is in keeping with the monistic point of view expressed in current psychosomatic medicine which holds that mental activity is a biological process. The authors stressed that this syndrome stood squarely between uncontested cases of psychoneurosis and non-neurotic wounded patients when both groups were viewed in terms of family history and symptomatology.

The last Supplement of the Army Medical Bulletin published recently is a monograph on combat psychiatry (4). The contributors stress the view that the military environment may evoke certain reactions which must be regarded as appropriate and normal, in spite of the fact that they would appear abnormal in a civilian setting.

The list of these situationally "normal" symptoms is most striking: 1) fatigue; 2) sweating; 3) palpitation and tachycardia; 4) precordial pain; 5) pain in

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chest; 6) respiratory difficulties; 7) urinary frequency and nocturia; 8) anorexia and nausea, to mention a few.

If these manifestations (are they manifestations of anxiety or of neurocirculatory asthenia?) were treated as appropriate to the situation, and these soldiers are commanded to cope with them as their comrades do, this was often the last that was heard about the complaints. To do otherwise would be like excusing a student from an examination because of anxious apprehension. If the men were invalided, the secondary gain and anxiety resulting from the sanction by authority fixated the process. An irreversible reaction was established which was maintained by guilt, considerations of prestige, and the need to justify the removal from a stressful life situation endured by others. It was further asserted that when the combat reaction could not be handled by the soldier, it was in relation to disabilities which were incapacitating in the civilian setting as well.

A few words should be stated about the variants of organ choice in neurocirculatory asthenia or anxiety neurosis.

Anxiety, as Dr. Oppenheimer has explained, is a non-specific reaction. Patients with anxiety, however, will differ in their presenting symptoms for reasons which have to do with the development of their personalities and with cultural pressures at the onset of their illness. Should the examining physician systematically question such a patient concerning the presence or absence of complaints referable to various organ systems, he will find that all the symptoms tend to be present. The patient decides which particular symptom is the most terrifying and the most productive of a secondary or reactive anxiety.

With these considerations in mind, two brief illustrative and contrasting case histories of patients are presented. Both of them would have been diagnosed as neurocirculatory asthenia or anxiety neurosis depending on who saw them. It might also be added that had one of the patients been seen by a urologist, a third diagnosis might have been brought into the picture, and if the second patient had been seen by a less thoughtful cardiologist, a fourth diagnosis would have been involved.

The *first patient* came for psychiatric consultation with the presenting symptom that he was unable to urinate. It was quite obvious that in addition he was suffering from all of the somatic symptoms of anxiety which have been mentioned. Although he felt that this anxiety was appropriate to his urinary difficulties, he could not differentiate between the precipitating anxiety and the reactive anxiety.

It turned out that the inability to urinate meant that the patient would not void when he thought he ought to. He never waited for the sensation of a full bladder to signal the need to empty it. He attempted to void by the clock. In other words, he strained to make a partially involuntary function completely voluntary. Behind this compulsion was the patient's conflicted confusion about two functions of the penis, viz., micturition and ejaculation. Ejaculation due to masturbation which he practiced compulsively was regarded by him as completely involuntary. The over-determined need to inhibit masturbation and the consequent ejaculation originated from the unacceptable guilt-provoking



sadistic fantasy which accompanied his onanism. In addition, he unconsciously equated the involuntary seminal pollution with fecal incontinence. He attempted to displace on to urination a fantasy of self-control which he was unable to apply to ejaculation. His precipitating anxiety, therefore, was in relation to unconscious and unacceptable aggressive impulses. His secondary anxiety was a reaction to his primary neurotic urinary symptom.

The *second patient*, a so-called cardiac case, was a man in whom a diagnosis of heart disease had been made on the basis of his symptoms of neurocirculatory asthenia. Despite the fact that a more experienced consultant assured him of the absence of organic heart disease, the patient clung to the incorrect opinion of the first physician whom, incidentally, he avoided seeing again. It was apparent that he had repressed the anxiety that focused his attention on his heart and came to believe that his symptoms were an appropriate response in a man who had severe heart disease which would cause a sudden, unexpected, untimely death. His psychotherapy disclosed that this death fear was at the root of his precipitating anxiety. The etiology of the whole picture was discovered in his repressed and therefore unconscious hostility towards his father who had fallen down a flight of stairs and was killed—a sudden, unexpected, untimely death. This kind of death carried with it the fantasy of punitive capital execution—and this, in turn, meant that a crime had been committed. The patient was coping with the problem of being magically punished for the magical execution of his death wish against his father. His anxiety was due to his effort to avoid a punishment—a cardiac death; i.e., death by execution. In other words, the second patient was in danger of becoming aware of his unacceptable aggressive impulses.

The reason that the heart is most often the organ to which the symptoms of anxiety are attached comes from the average patient's naive conviction that the heart is the organ of life and of love. This is especially true in individuals in whom the unconscious wishes or impulses underlying the anxiety have to do with aggression, destruction or death. It is the patient's fantasy of function which he attaches to a given organ which may determine the degree of disability he will display when that organ is affected. This fantasy of function, incidentally, is rarely influenced by logical explanation, arguments or sophistication. Physicians and other medically informed people do not acquire any immunity which will inhibit the somatic concomitants of anxiety neurosis. Any or every organ system may be involved in the state of anxiety neurosis. Although most of the symptoms represent pathophysiological activity, it should be realized that secondary and fixed pathological anatomy can result. When this occurs, this new condition in the pathogenesis of the disease requires a shift in the therapeutic management of the given patient. In any event, the value and emphasis on psychotherapy must be weighed in the light of psychological, physical and environmental factors in the disease state under consideration.

Anxiety neurosis, therefore, is a psychosomatic disease with protean manifestations. Essentially, it is a disseminated disease process which achieves a somatic pseudo-localization through the patient's emphasis on a particular symptom and the occasional iatrogenic attitudes of his physician.

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## THE CARDIAC PATIENT AND OPERATION\*

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In recent years there has been growing optimism in the prognosis of patients with heart disease, particularly coronary occlusion. We have been impressed with this optimism in relation to the cardiac patient undergoing surgical procedures, no matter how serious (1, 2). In the past both physicians and surgeons have been apt to avoid operation in cardiac patients unless it was obligatory and surgeons are wont to attribute some postoperative complications and fatalities erroneously to cardiac causes. Actually, we believe that, if certain precautions are taken to avoid anoxia, the compensated cardiac patient usually does almost as well as the one without heart disease. When necessary, or by error, operations of considerable scope have been successfully performed in patients with recent cardiac damage, e.g. acute coronary insufficiency or occlusion with infarction, heart failure, rheumatic fever. S. G., a man of 64, entered the hospital because of severe upper abdominal pain of several hours duration. A diagnosis of perforated peptic ulcer was made and a laparotomy was performed. No evidence of an intra-abdominal lesion was found. After operation, his condition was unchanged. An electrocardiogram showed the typical pattern of acute posterior infarction. His course was satisfactory until he sustained another occlusion three weeks later.

The cogency of these observations is obvious when one recalls the safety and frequency of total thyroidectomy in angina pectoris and heart failure, sympathectomy in hypertension and various procedures in congenital heart disease. To be sure, operation should be postponed, if possible, in the presence of recent infarction, status anginosus or congestive failure, but these conditions should not be considered contraindications to imperative operation. Similarly, in less urgent conditions or operations of choice, whether operation should be performed depends upon the surgical indication rather than the cardiac disease. Obviously, each operative procedure contemplated in a cardiac patient should be meticulously evaluated but should not be given up merely because cardiac disease is present. If there are definite symptoms of prostatism or biliary colic, for example, operation may be undertaken without undue trepidation in the presence of moderate or even advanced heart disease.

Actually, the surgical removal of an enlarged prostate, abscessed tooth, rectal fissure, inflamed hemorrhoid or gallstones often results in great improvement in the cardiac status, particularly angina pectoris or congestive failure. In such patients, operation should be urged. M. S., aged 54, had sustained a coronary occlusion and was followed in the cardiac clinic and in the hospital for a persistent, severe anginal syndrome. She also experienced frequent episodes of biliary colic and on two occasions was referred to the hospital for cholecystectomy. Because of the cardiac disease, this was deferred. Finally, however, the biliary colic became so severe that operation was performed. Her course was uneventful

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and during the following two years her anginal syndrome was mild or absent for long periods.

Preoperative consultation between the cardiologist, surgeon and anesthetist is well rewarded. In general, patients with hypertension or chronic rheumatic cardiovascular disease, particularly aortic insufficiency, tolerate operation best among cardiacs, but aortic stenosis is more uncertain. In complete A-V block also, the risk is usually greatly increased but we have observed major procedures carried out with great success. Renal disease is of serious significance.

The incidence of myocardial infarction following operation in patients with coronary artery disease has not been determined but it is our opinion that it is less than is commonly believed and that it can be reduced further. In a great many postoperative complications presumed to be the result of myocardial infarction, other causes are found, particularly pulmonary embolism. Infarction after operation is usually the result of coronary insufficiency without thrombosis and consists of subendocardial necrosis. The electrocardiogram shows RS-T depression and T-wave inversion which usually disappear after a relatively short period, i.e. one to two weeks (3). Instances of post-operative coronary occlusion with through and through infarction are encountered, as evidenced by Q-waves and RS-T elevation in the electrocardiogram. Whether these cases are the result of the operation or are coincidental is not clear (4). It must be remembered that not infrequently after operation marked T-wave changes appear in the electrocardiogram in the absence of any clinical or laboratory evidence of cardiac damage; indeed, these patients are often asymptomatic and ambulatory.

In operations on cardiac patients, the major consideration is to avoid anoxemia and coronary insufficiency. Therefore, the anesthesia must be carefully selected and administered and hemorrhage and shock must be prevented or treated promptly.

#### ANESTHESIA

This includes adequate preoperative sedation. Nitroglycerin and Dilaudid are beneficial for anginal pain. A combination of morphine and scopolamine in the ratio of 25:1 has been advocated just prior to operation. The choice of anesthetic must be individualized and should be influenced by the experience of the anesthetist. In the absence of congestive failure, a general anesthetic for conditions above the pelvis or a low spinal anesthesia for pelvic operations is preferred. In order to avoid anoxia, a high concentration of oxygen should be administered with the anesthetic and quick-acting agents are preferable, to avoid struggling during induction. In minor and extra-peritoneal procedures 2-3 per cent sodium pentothal by vein with 100 per cent oxygen is usually effective. In intra-abdominal operations ether is preferred by many but a cyclopropane-oxygen has been suggested for induction; thereafter, the percentage of cyclopropane is reduced and traces of ether are administered to overcome the tendency of cyclopropane to induce arrhythmias (5).

The cardiac patient requires careful watching during the immediate post-



operative period, particularly if general anesthesia other than pentothal has been used. G. B., a middle-aged man with a severe anginal syndrome, underwent cholecystectomy well and was in good condition after being brought to his room. Later on, while emerging from the ether anesthesia, he vomited a good deal and developed coronary insufficiency which terminated fatally. Autopsy revealed severe coronary sclerosis but no occlusion. It is possible that closer supervision post-operatively might have prevented the fatal outcome. For example, oxygen therapy during this period may be beneficial.

When congestive failure exists or has been present recently, spinal anesthesia is preferred since it produces peripheral vasodilatation, achieving the effect of a bloodless phlebotomy. For this reason, it has been suggested for the treatment of persistent pulmonary edema. In order to prevent a drop in blood pressure, particularly in patients with coronary disease, spinal anesthesia may be preceded by 5 to 15 mg. of neosynephrin intramuscularly or 2 mg. in a very slow, continuous intravenous drip, and accompanied by 100 per cent oxygen. Occasionally these precautions are unnecessary. S. S., a man of 80, exhibiting symptoms of prostatism for a number of years, and an anginal syndrome for one year, experienced a myocardial infarction with coronary insufficiency. There was mild pulmonary congestion. During the ensuing month his prostatic symptoms increased in severity. Although he complained of repeated anginal pain, it was considered necessary to perform a transurethral resection. Spinal anesthesia was given and the operation lasted ninety minutes. There was no change in the patient's condition at any time. His blood pressure was 120 systolic and 80 diastolic prior to operation and did not fall below 100 systolic and 60 diastolic throughout the procedure.

In congestive failure digitalis should be administered pre-operatively and post-operatively. It is probably not advantageous to give digitalis routinely in all cardiac patients.

Paroxysmal arrhythmias are a very common complication of anesthesia and operation, particularly cyclopropane in the presence of adrenalin. The majority of arrhythmias under anesthesia offer little difficulty since the supraventricular tachycardias frequently are stopped by carotid sinus or eyeball pressure, and ventricular tachycardia usually responds promptly to the rapid intravenous injection of 5 cc. of 1 or 2 per cent procaine (6) or 0.450 Gm. quinidine lactate intramuscularly. The oral administration of 1 Gm. of procaine amide prior to operation may prevent ventricular arrhythmias. Intramuscular quinidine is often effective also in auricular fibrillation and flutter; if not, a digitalis glycoside, such as cedilanid, or 20 cc. of 20 per cent magnesium sulfate may be given by vein.

A history of paroxysmal arrhythmia is not a contraindication to a required operation. In such patients the pre-operative preparation should include quinidine sulfate in adequate dosage or procaine amide. In such patients, ether is considered the anesthetic of choice combined with oxygen.

The presence of permanent auricular fibrillation or flutter, in which the ventricular rate has been controlled by digitalis, usually offers no difficulty to the surgeon. Occasionally a patient is seen with auricular fibrillation and a ventricu-

lar rate of 80 or less without digitalis. In such patients no therapy is required since a significant change in rate usually does not occur during operation in the absence of digitalis. We have also observed operations performed uneventfully in patients in whom these arrhythmias are of recent origin and control with digitalis is still incomplete. B. H., a man of 68, was seen in a recurrent episode of auricular flutter. The ventricular rate was 120. The arrhythmia had usually responded to digitalis but on this occasion persisted. Nevertheless, prostatic operation was considered imperative and was performed without any deterioration in the cardiac status.

To prevent or correct coronary insufficiency and shock attending loss of blood during operation, transfusion is of the utmost importance. If bleeding is anticipated, the transfusion should be started at the beginning of the operation and it should be continued after its completion, if necessary. It should be given slowly to avoid pulmonary edema, which occurs rarely. Should the latter set in, relief is usually obtained by the routine treatment, including an intravenous mercurial, and terminating the transfusion. In the presence of congestive failure, washed red blood cells should be used instead of whole blood. In cardiacs, excessive fluids should be avoided generally.

Following operation, antibiotics are important in preventing infection which tends to produce congestive failure. We have also suggested the prophylactic use of penicillin prior to operation in all persons with a definite cardiac murmur, including an apical systolic (7).

In the presence of phlebitis or congestive failure, dicumarol is indicated to prevent pulmonary or peripheral embolism; it may be started one day after operation.

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## PSYCHODYNAMIC FACTORS IN SURGERY\*

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On a surgical service the operative procedure often functions as the nucleus about which psychiatric problems are elaborated. The anticipated operation becomes closely invested with the patient's fears, anxieties and wishes, and may precipitate a critical emotional climax. It may also serve as a backdrop upon which sundry unconscious motivations, needs and defenses are portrayed. The specific psychiatric disturbance is therefore the result of complex interactions of the varied and diverse forces struggling for expression within the individual.

Most patients face operation with a mixture of resentment and annoyance and, depending upon the nature and severity of the procedure, a measure of anxiety and apprehension. To some, however, it may serve as a welcome respite from the tedium of work or household responsibilities. Others will find in it a transient escape from an intolerable marital or sexual situation. To a few it may, for a time, provide a sense of importance through the prestige attached to hospitalization and surgery. The harried individual, oppressed by mounting responsibilities and an inconsiderate family, may thus achieve a privileged role. In some instances, convalescence from operation may be indefinitely perpetuated as a specific secondary gain. Many patients envisage the approaching operation as a death threat, usually with no relation to reality. Severe pre-operative panic states may be precipitated by the dread of anesthesia as well as possible mutilation or loss of function. Such all-pervading fears undoubtedly motivate the many who turn to cultists and charlatans who promise relief or cure without surgery. We are also familiar with a fairly numerous group who welcome operation as a convenient and socially acceptable means for expiating their sins, conscious or unconscious. In extreme instances, a true "operation addiction" ensues which may be interpreted as a desire for progressive self-destruction. These are the individuals who engage the services of a surgeon to inflict the punishment that satisfies their sadomasochistic needs.

### REVIEW OF LITERATURE

With a few outstanding exceptions, the psychiatric literature contains very little dynamic material in relation to surgery. Most observers are preoccupied with the more obvious emotional responses of the individual to operation. Little attention has heretofore been focused on the patient's deeper character structure and his earlier reactions to stress. The specific stress situation presented by an operation may be compared in its intensity to such previously experienced traumata as a prior operation, loss of a love object, childbirth and the myriad and complex problems presented by the vicissitudes of psychosexual development.

Helene Deutsch (1) records observations culled from many years of psycho-

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analytic experience in the course of which memories of operations and their emotional associative links recurred. She discusses psychic reactions to surgery from a number of standpoints: a) the psychology of the individual and the emotional situation prior to the operation, b) the meaning of the procedure including the significance of the anesthesia, c) the post-operative reaction and d) the patient's relationship to the surgeon.

The importance of pre-operative preparation for the prevention of anxiety is stressed especially in terms of avoiding post-operative symptoms of "fright neurosis". The patient's conscious fear reactions to an operation are often not commensurate with the real dangers mobilized by the external operative threat. The dangers may be two-fold: a) fears involving anesthesia in which loss of consciousness is equated with death and b) those fears related to bodily injury or attack which may reawaken childhood dreads of bodily mutilation referred to as "castration anxiety". It is chiefly in chronic disease that fantasies may be related to the organ involved. These may in part be determined by the organ's location, function or the symptoms referable to the illness. Thus the symbolic meaning of a given organ which is to be operated upon may directly influence the patient's subsequent course.

The patterns established in earlier operative experiences, especially those in childhood, are characteristically repeated in adult life. In women the relationship between an operation and childbirth is clearly seen in the reactivation of anxiety involving the patient's relationship with her mother. Guilt from death wishes directed toward her mother or murderous fantasies about the unborn child may lead to the masochistic turning of the aggressions against oneself and thus in turn to a fixation on post-operative symptoms and suffering. Post-operative dreams frequently disclose the ambivalent wish for life and the longing for death.

It is not the presence or absence of the pre-operative anxiety which determines the prognosis, but rather the patient's capacity for "inner assimilation" of the anxiety signal. The goal of this assimilation is the building up of inner defenses to protect the ego from fears associated with the operation. These fears may be realistic or objective and may be directly associated with castration anxiety, especially in conditions where the organ itself is connected with various fantasies. Further, psychic determinants may have been identified with the ailing organ prior to its manifest disease, and may possibly have played contributory etiologic roles. Such organ predispositions may be generalized in character or more specific in their implications. For example, the threatened loss of sight may provoke a multitude of emotional responses related to the physiologic function of the organ as well as its psychologic implications. Among the latter, partial components of the sexual drive such as scopophilic erotization of the visual apparatus may determine the operative responses.

Szasz (2) in a psychiatric study of patients treated with vagotomy for peptic ulcer, found a small number who, despite the disappearance of all roentgen evidence of the disease, experienced a return of classical ulcer pain after variable periods. Although the return of symptoms following vagotomy has been in-



terpreted by clinicians as due either to persistence of the ulcer in the absence of roentgen evidence or to a "functional bowel disturbance", Szasz hypothesizes that the syndrome may be classed as a "phantom" sensation. He believes that the mechanism of the persistent pain is closely analogous to the phantom pain following limb amputation. He cites 2 instances of post-vagotomy ulcer pain in which the ulcer syndrome was present for a great many years and postulates that the long continued perception of pain as well as the prolonged rituals identified with its treatment had led "the ulcer" to become part of the "body image" i.e. the symptom complex had been literally incorporated into the patients' egos. He further stresses the fact that neither patient "resented" his symptoms, appearing to enjoy his diet and may have thus found an answer to a narcissistic need in his illness. He quotes Fenichel, who believes that the creation of the body-image is the result of outer tactile and inner sensory data in which the individual, his organs or even his possessions become something sharply apart from the rest of the world. Although visceral organs are not, ordinarily, represented in the body-image, Szasz believes that the prolonged perception of a sensation may ultimately become the necessary sensory stimulant for a corresponding mental representation and thus produce a "visceral phantom pain". Although Freud has not specifically referred to this phenomenon, he clearly describes the psychic processes involved in the evolution of phantom pain.

Menninger (3) analyzes the covert neurotic traits of some surgeons which may betray themselves in the form of a sado-masochistic urge to operate in the absence of clear-cut indications. Many surgeons are not unaware of the motivations inducing such behavior and have bitterly denounced surgical cruelty and unnecessary operations. Although some surgeons will yield for meretricious, or even materialistic, reasons to the patient's insistent demands for operation, there are some instances when the patient may succeed in making the procedure appear imperative. In these cases there is a compulsive submission to operation rather than a physiologic need. He mentions Jelliffe's reference to a woman in whom the "repetition compulsion" led to 28 different operations in various parts of the body before the age of 21. In some instances such operations may actually produce therapeutic results. He refers to Freud who, in "Beyond the Pleasure Principle", cites the relief or amelioration of traumatic neuroses, depressions and schizophrenia through disease or injury. Surgical operation may similarly be included as an unexpected and dramatic stimulus whereby unmanageable quantities of libido are stimulated. It is *par excellence* in plastic surgery that repeated demands for operation for minimal or nonexistent defects indicates a craving for psychologic rather than physical repair.

In the formulation of the prevalent motives and mechanism for operative demands, Menninger describes 4 unconscious motivations for compulsive submission to operation. First, the need to avoid facing a situation which is feared more than surgery. In this flight into surgery there is a "bribery of the conscience" in which the surgeon represents the person who is designated to assume the responsibility. The patient may often seek operation as a substitute for psychotherapy and in some instances may thus secure relief. The second motive

determining the choice of operation is the transference to the strong, dynamic or even ruthless surgeon as an authoritative father figure. When there is an intense craving for father love, the patient's masochistic component can accept it solely in the form of pain. A third, and frequently observed motive, is the desire for operation which would answer the fantasied wish for a child. This is especially observed where the Caesarian concept of birth is well developed. The fourth type of satisfaction in the unconscious desire for operation is the wish to be castrated or, more specifically, the wish to be relieved of anxiety by submitting to castration. In this wish there are at least 2 elements: a) the need for punishment and b) its erotic capitalization through masochism, exhibitionism, etc. The patient thus atones for his crime and converts himself into an emasculated feminine person more capable of receiving love from the avenger. There are occasional instances when the patient demands partial, and even repeated, genital resection. In psychotic cases, self-castration has been observed or may appear in the guise of a demand for castration. It should be stressed that the desire for castration is not to be confused with self-destruction but rather as the avoidance of death by the sacrificial offering of the phallus, the *part*, rather than of the *total* personality. The genitalization of various parts of the body as described by Ferenczi and Freud may explain this wish for castration. Further, the patient can, through the punitive situations created by repeated operation, vent his passive aggression and perhaps attain the love he has been otherwise denied. In considering the motives underlying the desire for operation, the author cites the primary gains viz. the freedom from responsibility, the attention, sympathy and devotion of family and medical attendants as well as the desire for love which is thereby obtained.

Greenacre (4) describes the apparent paradox provided by the pain of repeated operations, in some instances even involving the removal of organs and/or consequent disfigurement, and the unconscious emotional gratification thus obtained by the escape from underlying anxiety which offers a more acceptable solution, albeit a temporary one. The operation thus substitutes a specific conscious fear which the patient unknowingly substitutes for the vague indefinable conflicts which threaten to overwhelm him. This substitution further permits him to regress to a dependent child-like state in which he can unashamedly demand the attention, affection and interest which he craves. The utilization of surgery as a suggestive therapeutic procedure when operative indications are minimal or non-existent, creates the risk of evoking a pattern of habituation to operation.

In a study of 23 cases of post-operative psychosis at the Bellevue Hospital, New York, Abeles (5) found that the majority fell in the 3rd to 5th decades and that a considerable proportion followed operations on the genital organs and thyroid gland. Confirming the observations of others, he noted that the psychoses appeared in from 1 to 15 days following operation with the greatest concentration between the 3rd and 5th days. Some authors have attempted to link the time of the appearance of post-operative psychoses with the peak of protein destruction which is usually reached on the 3rd day following operation. The

symptomatology generally consists of a combination of confusion, delusions, hallucinations and disturbances in motility. The duration of the psychoses tends to be variable but most of them subside within a few days or weeks; unusual prolongation of symptoms beyond a period of several months suggests the presence of an organic psychosis or schizophrenia. As the syndrome usually represents a continuation of the patient's entire life history and previous experience, knowledge of his family background, intellectual level, previous operations and pre-psychotic state are essential for adequate evaluation. The patient's fear of operation may, in some instances, be so intense that a *pre-operative* psychosis may be precipitated. In other cases, the pre-operative setting may be such that the operation merely represents the high point or crucial incident in the evolution of a post-operative psychosis. Apprehension may thus be induced by the fear of operation and death and often provoked by the forbidding hospital atmosphere, the impact of the operating room and the dread of losing consciousness through anesthesia. A very important factor in the post-operative syndrome stems from deeper fears of castration, mutilation and dismemberment.

The importance that the patient attaches to the organ involved can influence the content of his thoughts and many authors have stressed the disproportionately large number of post-operative psychoses following gynecologic and testicular procedures. Non genital organs may, through certain symbolic distortions or displacements assume gonadal roles, e.g. the eyes; their vital role in perception of the environment further accentuates their significance. Post-anesthetic psychoses can at times be distinguished from the more common post-operative psychoses by the almost immediate precipitation of the symptoms in the former and the relatively brief period of delirium. Confusional syndromes have followed most forms of anesthesia and are sometimes even observed following the spinal route. Another source of post-operative disturbance resides in the upheaval induced by operation in the chemical and metabolic hegemony of the body. This includes acidosis, alkalosis, acetonuria, glycosuria and hypoglycemia. Transient hepatic and renal insufficiency have been implicated in post-operative psychoses. Vascular disease, with or without hypertension, intestinal disturbances with malabsorption, avitaminosis and toxic-infectious factors may induce similar post-operative psychotic states. The use of both pre- and post-operative sedation must be circumspect lest its influence alone create a psychotic trend. It is thus apparent that with such a constellation of organic and chemical factors, the operated patient is exposed to profound and varied traumata.

Lindeman (6) studied 40 women subjected to operation and found that 25 presented no new complaints following the procedure. Fifteen women, however, developed symptoms after a period of 3 weeks. These cases are to be differentiated from those with acute post-operative delirium reactions. He found the proportion of emotional responses to be distinctly higher in pelvic procedures, chiefly hysterectomy, than in operations in the upper abdomen.

Lipkin and Joseph (7) cite some of the commoner anxieties attending surgical procedures e.g. fear of disfigurement, loss of function, and threats to socio-economic security. Concrete suggestions for the management of preoperative in-



interviews are given. The authors feel that it is desirable to stress the simplicity of the procedure and emphasize the reduction in post-operative pain through improved therapeutic techniques. Specific fears involving disability, reduction or elimination of sexual function, permanent colostomy and other operative sequelae are met with simple explanation, reassurance, interpretation and encouragement. The authors emphasize the need for enlightening surgeons in the recognition of potential psychiatric disturbances. The achievement of emotional security during the post-operative period depends largely on individualization in the management of the patient's emotional and medical needs.

Preu and Guida (8) in a study of psychoses complicating recovery from cataract extractions find that serious mental disturbances follow 3 per cent of such operations. The authors have the impression that despite the absence of specific evidence, psychoses are more frequent in ophthalmologic than in general surgery. The grave danger of mental disturbances following eye operations has been repeatedly stressed and may even lead to irreparable damage to the eye. A report of 4 cases of psychoses complicating recovery from operations for cataract are discussed in detail. In no instance had there been any evidence of a preceding emotional or mental disturbance nor any adverse response to previous non-ophthalmologic surgical procedures. In a setting of darkness, panic occurred in from 2 to 5 days following operation, associated with confusion and paranoid misinterpretation of the environment. The clinical picture appeared to be purely psychogenic and not on the basis of an organic delirium. In one case the psychosis subsided within 24 hours after removal of the bandage from the untreated eye. In the second, a man of 56, no abnormal personality features were present, but in an atmosphere of darkness, he became apprehensive, suspicious and confused; the symptoms rapidly subsided after removal of the bandage from the untreated eye. In the third case, a man of 83, who was excited and apprehensive on admission and who had been emotionally unstable all his life, extreme paranoid manifestations appeared on the second post-operative day. The acute psychosis subsided 48 hours after removal of the bandage from the untreated eye and the residual picture returned to that preceding operation. The fourth case, a woman of 74, had manifested gradual mental deterioration several years preceding operation with intermittent confusion, especially at night. Several days following the extraction of the cataract, she became restless, confused and disoriented. There was no residual impairment in her mental status following removal of the bandage from the untreated eye. A differentiation is made between psychogenic panic induced by the emotionally disturbing effect of the post-operative setting of darkness and the accentuation of confused, or psychotic trends previously present in aged arteriosclerotic patients. The removal of the bandage will, in most instances, relieve symptoms except in those with long standing histories of disability e.g. the organic type of psychosis. Control can, to a considerable degree, be effected by operating on the patients in their own beds or even at home to calm their fears and suspicions. Early removal of the bandage from the untreated eye is of importance. The dangers of the excessive use of sedatives are also stressed.

Ebaugh (9) emphasizes the surgeon's approach to the whole individual rather



than to an inert container of offending viscera. He points to the need for closer, sympathetic and more understanding surgeon-patient relationships, with the avoiding of tactless and fear-inspiring comments. This enlightened approach should include an attempt to understand the patient's personality, his emotional and family background and the meaning of the operation to him. Adequate investigation of the patient's personality endowment and experience will go far to prevent unnecessary surgical intervention as well as the frequently encountered emotional sequelae. The psychological hazards of the post-operative period are described, as well as the disproportionate anxieties invoked in both sexes by genital procedures and limb or digit amputations. The maintenance of adequate nutrition and hydration and the judicious use of sedation are essential in preventing toxic or delirious post-operative states. A simple, understandable and sympathetic formulation should adequately prepare the patient for the operation as well as help adjust him to the hospital environment and procedures. Operations of choice should be deferred or avoided in an emotionally disturbed person and, should it be found imperative, the patient should receive adequate psychotherapy.

#### OPERATION PHOBIA

Within recent years, the medical literature has focused increasing emphasis on consideration of the patient's "total personality" in the adequate management of disease. Most physicians are now becoming aware of the role of childhood experiences in determining affective reactions and behavior patterns in adult life. The comprehensiveness of such an approach is, however, often obscured in those instances where structural disease is clearly manifest and when surgery offers a simple and rapid means for correcting or alleviating the ailment. The bewildered and anxious patient who is not psychologically prepared for what he deems a severe bodily threat, may develop a post-operative emotional disturbance. In some extreme anxiety or panic states, the pre-operative period may also be severely complicated and the patient may stubbornly resist urgently indicated surgical procedures. The following case graphically illustrates the problems arising from a severe operation phobia.

R. S. a 35 year old married man was referred to the psychiatric clinic in April 1947 because of his fear of submitting to an indicated pulmonary operation. Symptoms of lung disease first appeared in 1940 with hemoptysis; all studies, however, proved negative. Three years later he had an acute viral pneumonia which rapidly resolved without complication. A short time later he was gassed by chlorine while working in a paper factory and developed an acute pneumonitis with intermittent hemoptysis. He was in the hospital for 6 weeks and on discharge was told that he had residual consolidation in the right upper pulmonary lobe. In the next 4 years he was hospitalized a total of 8 times because of recurrent episodes of pneumonia accompanied with fever, purulent sputum, chest pain and occasional hemoptysis. At each occasion his symptoms were controlled with bedrest and medication.

During his first hospital stay in January 1944, a chest x-ray showed irregular

consolidation of the right upper lobe with displacement of the mediastinum to the right. The patient refused bronchoscopy and left the hospital against advice. Some months later he was finally induced to accept the examination which disclosed thick, malodorous pus oozing from the anterior branch of the right upper lobe bronchus with free bleeding. The suggestion of another bronchoscopy provoked extreme agitation and he again insisted on leaving the hospital. Impatient at the delay in securing his belongings, he precipitously left the hospital only partially clothed. A few days later he left for Nevada, leaving his wife and 3 children in New York. He showed sufficient improvement to be able to resume work. Inducted into the army in 1945 his symptoms promptly reappeared and he was discharged as a psychoneurotic. Shortly thereafter, a bronchogram disclosed an obstruction in the same bronchus with a persistent shadow in the lower part of the right upper lobe. He visited several clinics but whenever operation was recommended, he fled. During this time his family was on relief and he complained of frequent headaches, insomnia and irritability. He finally agreed to accept psychiatric aid in April 1947. After sporadically attending the psychiatric clinic for about a year, he indicated his willingness to submit to operation with the following conditions: a) he was not to know when the operation would take place, b) he was to have a general anesthetic administered on the ward so that he would not see the operating room and c) the psychiatrist was to be present at the operation. He was admitted to the psychiatric in-patient ward and on the following day became infuriated because the nurse had given him an injection "in a bad way"; he also complained loudly about his roommate. He showed considerable apprehension because of a large shrapnel scar on his neighbor's back but when this was analyzed, his agitation subsided. Following a preliminary anesthesia on the ward, a right upper lobectomy was performed in February 1948. A chondroma of the bronchus with chronic pneumonitis and cylindrical bronchiectasis distal to the lesion were found. He made a rapid recovery and was discharged within a month.

During the psychiatric interviews, it became increasingly apparent that his fear of operation mirrored a life-long pattern. He recalled an incident at the age of 4 when his father took him to a hospital for a laceration over the right eye. When he heard that sutures were to be used and he caught sight of the needles, he fled from the hospital in panic and hid in a park for 12 hours until hunger and cold forced him to return. He also recalled with remarkable clarity an accident in which one sister injured another's eye while sharpening a pencil with a kitchen knife. At about the same time, he vividly remembered that while on a swing the edge of the seat struck his mother's eye and tore her right eyelid. Both these episodes occurred just prior to his own eye injury. At the age of 7 he fell on a piece of metal, lacerating his back; although he bled profusely he allowed no one to touch him or even wash the blood away. Another clearly defined recollection at this age occurred in a dispensary when he saw a man being catheterized; his own terror at the sight was vividly recalled. At 12 he agreed to undergo a nasal submucous resection after the nature of the procedure was fully explained to him. His nose was anesthetized but when he noted "the

gleaming metal" on the instrument tray he was seized with panic. Using a ruse of going to the toilet, he picked up his clothes and escaped. For the following 20 years he often contemplated having the operation but such thoughts were laden with great anxiety. A few years later a similar incident occurred when he anticipated tonsillectomy. On the evening before operation he stole out of the hospital and shortly thereafter left home. In all these episodes he seemed to accept the need for operation, was eager to cooperate but was emotionally blocked. The mere mention of an operation or the sight of a scar would precipitate an acute anxiety attack with palpitations, insomnia and extreme irritability.

The patient was the youngest of 3 children and the only boy in a poor Jewish family. His father showed little domestic interest and his job as a ship's steward kept him away from home much of the time. When the patient was still a child his father contracted syphilis and transmitted it to his mother. Frequent blood tests were required of the whole family. He always showed preference for his mother and would refuse to accompany his father to ball games. He earned extra money selling newspapers and would regularly give it to his mother. She was a religious, hard working woman who singled him out for special devotion. During her terminal illness with luetic heart disease she was in the patient's home when her respirations suddenly became labored. He frantically rushed out in an attempt to secure oxygen. On his return he was told that she had died and throwing himself on her body, made violent efforts to restore life by breathing into her mouth. He was finally forcibly removed by his family. He has since visited her grave whenever crises occurred in his life. His mother has often appeared in his dreams and he feels that her spirit protects him. His older sister served as a mother surrogate in his early adolescence. In discussing her, she is often confused with his mother. Although he insists that he likes her husband he finds it impossible to avoid bickering with him, criticizing him at every opportunity.

He was a bedwetter until the age of 10. He received no sexual instruction at home. Nocturnal emissions began at 14 but he recalls no fantasies. He began to masturbate at 15 and the next year had coitus with a prostitute. At 18 he courted a girl of 14 and a year later they were married. Sexual relations with his wife were presumably satisfactory until about 3 years ago when he experienced headaches, insomnia and irritability with frequently recurring dreams of lobectomy and operative death. It was at this time that premature ejaculations appeared.

Although most patients meet the prospect of a major, and often dangerous procedure such as lobectomy with a measure of justified apprehension, this patient's fears were greatly exaggerated due to earlier traumatic experiences. The institution of adequate psychotherapeutic measures finally helped him to secure a proper perspective which finally allowed him to accept operation. Whenever a situation arose which carried with it the possibility of bodily mutilation, his behavior characteristically repeated the pattern established at the age of 4 when his eye was injured. At this age a child is usually at the height of his Oedipal conflict and the fear of injury to the genital is paramount. The patient's life is replete with indications of an unresolved sexual triangle in which his

unconscious incestuous love for his mother (or his older sister, as a mother surrogate) is coupled with his hatred and fear of his father (or brother-in-law). The symbolic significance of the eye as a genital is well known and recalls the myth in which Oedipus blinded himself (or, as in some versions, castrated himself) for his incestuous union with his mother.

#### THE PSYCHOSOMATIC APPROACH

F. M., a 33 year old bartender was admitted to the Mt. Sinai Hospital in October 1943 with a 4 year history of duodenal ulcer. A gastroenterostomy had been performed in 1940 because of partial obstruction. Three weeks prior to admission, severe watery diarrhea and finally fecal vomiting appeared; he had lost 26 pounds in 6 months. The presence of a gastrojejuno-colic fistula was determined by a methylene blue enema. A stool guaiac test was negative for blood. Accordingly a first stage glass rod ascending colostomy was performed for fecal diversion. After a stormy course with localized peritonitis he slowly improved and a second stage procedure consisting of subtotal gastrectomy, jejuno-jejunostomy, repair of the opening in the transverse colon and a jejunostomy for alimentation was performed. A jejunal ulcer was found at the previously anastomosed site and another ulcer was found in the efferent jejunal limb which had perforated through the mesentery of the jejunum. A large lymph node was removed from the lesser omentum and on histologic study proved to be a *metastatic carcinoma simplex* with an undetermined primary site. His post-operative course was smooth and on discharge he was comfortable and the ascending colostomy functioned well. During his second admission a week later he complained of some abdominal pain but this rapidly subsided and the colostomy was closed.

He was readmitted in April 1946 because of a brief history of epigastric pain following meals. Gastroscopy disclosed a severe gastritis. A psychiatric consultation was requested during which the patient discussed problems which were causing him severe emotional stress. With superficial psychotherapy directed primarily toward permitting him to express his feelings of hostility and resentment he soon improved and was able to leave the hospital.

In July 1946 he was again admitted because of pain in the left upper abdominal quadrant and lower left chest which was unrelated to food or respiration. Physical examination and roentgen studies of the stomach and chest were negative. He soon, however, became a problem in ward management as his complaints of pain and constant groaning disturbed other patients. On occasion he was given hypodermic injections of distilled water following which he seemed to obtain moderate relief. This led the resident staff to suspect that his symptoms were again on a psychogenic basis. While at home he had been given morphine to control pain and there was some question as to whether he had developed an addiction. His behavior became so disturbing that he was threatened with removal to a psychopathic hospital. In view of this another psychiatric examination was requested. At this time he was found depressed, unable to sleep and had lost weight. Although the pains he had described during his previous



admission bore a definite relationship to specific emotional irritants, the current distress was totally unrelated to psychological conflicts. In addition, his symptoms were not those of morphine withdrawal. When a member of the secretarial staff telephoned his mother-in-law to caution her that he might be sent to a psychopathic hospital if he did not quiet down, he became obsessed with the fear that this would, in fact, transpire. He was well oriented and showed no confusion or bewilderment. In view of these observations it was recommended that further studies of his physical status were indicated to determine the cause of the incessant pain. As part of an extensive investigation, a barium enema disclosed the presence of a filling defect at the distal end of the transverse colon. At exploration an inoperable carcinoma of the splenic flexure was found. The post-operative course was stormy and painful and he frequently required demerol.

This patient illustrates the danger of making a psychiatric diagnosis by exclusion. During his last admission his repeated complaints of pain in the presence of normal gastrointestinal roentgen studies led to invoking a psychogenic etiology with little evidence to sustain such a belief. The psychiatrist, unable to substantiate a psychogenic basis for the pain, advised further studies which ultimately disclosed the true nature of the disease.

It would be foolhardy to diagnose structural disease in the absence of suggestive symptoms or signs, yet this tendency is all too common where possible mental illness is suspected. The designation of a patient as neurotic should be deemed a diagnosis and not employed in a derogatory sense. Such practice merely reflects the inadequacy and frustration of the physician who has been reduced to name-calling, and may prove disastrous.

Conclusions as to pathogenicity following placebos e.g. injections of sterile water, are often unreliable. It is commonly recognized that suggestion or distraction will temporarily relieve pain caused by structural disease and such relief is in no sense pathognomonic of emotional causation. Such a diagnosis should rest on positive evidence indicating a personality disorder as a reaction to specific life situations, and a survey of the patient's personal history will usually reveal previous problems in adjustment and the presence of definite neurotic manifestations.

#### ORGAN SEXUALIZATION

A. B. a 36 year old white married Italian male was admitted to the Mount Sinai Hospital on March 10, 1947 with a 17 year history of ulcerative colitis. His first admission was in October 1930 because of a 2 month history of bloody bowel movements, abdominal pain and a loss of 40 pounds in weight. The onset corresponded with his mother's hospitalization for hysterectomy. During his 11 week stay at the hospital a diagnosis of ulcerative colitis was confirmed by roentgen and sigmoidoscopic studies. The hemoglobin had fallen to 42 per cent, all blood agglutination tests for specific dysentery organisms were negative and no ova or parasites were found in the stools. Treatment with bismuth, opium, calcium lactate and repeated transfusions gradually effected a reduction in the

bowel movements to 2 daily and at discharge the sigmoidoscopic appearance of the mucous membrane was almost normal. He had gained 13 pounds, the hemoglobin had risen to 68 per cent and he was relieved of abdominal pain.

He was asymptomatic until shortly before his readmission on March 27, 1931 when he had a migratory polyarthrititis and recurrence of frequent bloody bowel movements. His symptoms soon subsided and he was discharged at his own request. He was well for 11 years until shortly after the birth of his first child. He was working in a defense plant at the time and was disturbed by a feeling that, to his own detriment, partiality was being shown to German sympathizers. Subsequent exacerbations of bloody diarrhea appeared almost invariably with emotional strain, the most severe one at the birth of his second child, two and a half years prior to his admission. Two weeks before entering the hospital he suddenly experienced severe diarrhea with 20 to 25 watery movements daily and intense abdominal cramps. He was observed on the medical service where a barium enema examination revealed widespread ulcerative colitis involving the rectum, sigmoid and distal end of the descending colon. On sigmoidoscopy, the entire mucosa was found to be thickened, granular, friable and covered with a thick purulent exudate. He was transferred to the psychiatric service for investigation of possible psychogenic factors in his illness. Despite heroic efforts, medical therapy could not control the intractable diarrhea and he ran a persistently high fever with progressive weight loss, anemia and hypoproteinemia. Following a prolonged period of indecision, he finally consented to an ileostomy at which time the transverse colon was observed to be markedly inflamed. His response to operation was excellent with prompt remission of fever, gradual gain in weight, rise in hemoglobin and at discharge the ileostomy was functioning well. He has since had a subtotal colectomy with further improvement.

Psychiatric investigation disclosed that he was an only son and that soon after his birth his father emigrated to this country; he then developed an unusually close emotional relationship with his mother. He was a bed-wetter until the age of 5. When he was 8, they rejoined his father and he thenceforth felt neglected and deserted by the mother who no longer gave him the tender, loving care he had previously received. His college career was interrupted by his first illness and was never resumed. Sexual education was neglected at home and most of his information was gathered from his playmates. Masturbation with heterosexual fantasies began at 13 and persisted until 18 when it was discontinued because of increasing guilt feelings. He avoided girls because of an exaggerated fear of syphilis. A year later, and corresponding with the time of his mother's hysterectomy, his initial symptoms appeared. His first marriage, at 25, to a neighborhood girl, was loveless and lasted for but one month. He had apparently married her to show his gratitude to the girl's mother for saving him from gas asphyxiation when he was 9. After a space of 3 years he remarried, this time without the recognition of the church. He expressed the belief that the rectal bleeding was a form of "purification for the sin of remarriage". His second marriage has been stormy with frequent interference from his mother-in-law who insisted that her daughter be aborted soon after they were married. This was

done without the patient's knowledge or consent and he has since distrusted his wife which led to bitter quarrels. Following the birth of the first child, his wife was compelled to work and his mother took over the care of the children.

The patient was always perfectionistic, neat and meticulous, and was constantly concerned with finances and social acceptability. He was given to outbursts of rage against his wife and father but they were never directed to his mother. He maintained an infantile, dependent relationship toward her, repeatedly seeking her attention.

Soon after the operation both nursing and medical staffs observed that he had become intensely preoccupied with the care of the ileostomy stump, maintaining scrupulous cleanliness with fastidious care. He even demurred for a time, at the use of an ileostomy bag. On the occasion of one interview he volunteered to show the psychiatrist the operative site and then proceeded to massage the ileostomy protrusion with gauze pads; the stump was observed to become red, somewhat swollen and firm. He laughed excitedly as fecal contents began to flow and said "it's like when you rub down there". He seemed to derive considerable pleasure from having a 19 year old fellow patient assist him in the care of the ileostomy even though he was perfectly capable of doing it without help. On one occasion when the ileostomy stump appeared to be growing smaller, he expressed considerable anxiety lest it shrink further. When the psychiatrist remarked on his rapid gain in weight, he said that one of his motives in eating such large quantities of food was to have additional fecal material to clean and rub away from the ileostomy opening.

The onset of his illness was apparently related to the suppression of masturbatory practices and the threatened loss of his mother who was awaiting hysterectomy. It should be noted that prior to the operation he had exerted great pressure and perspired profusely during bowel movements; he likened this to "a woman having labor pains; I push and push to get the rotten stuff out of me". He had a number of additional birth fantasies. The incestuous attachment to his mother and the hatred of his father are the hallmarks of his unresolved oedipal conflict. The colitis served to heighten his infantile dependence and its attendant gratifications. The birth of his own children represented a threat by displacing him as a child and sole recipient of the attention of his mother and wife. The creation of an artificial orifice for fecal drainage allowed him directly to manifest his anal erotic fixation which had been previously repressed, appearing only in his symptoms and compulsive (anal) personality. The actual physiologic participation of the ileostomy in the sexualized fantasy of function through its acting as a phallus and its association with subjectively experienced orgasmic-like sensations, is a striking confirmation of Freud's theory of the libidinal cathexis of various organs. It should be stressed that the patient initially feared an operation and exacted a promise that he would be permitted to return to the psychiatric ward if he so desired. However, he never made this request following operation because he had meanwhile established a close attachment to the surgeon. The relationship to the physician who provided him with a permissible orifice to manipulate and thus secure gratification without associated guilt feelings, plays a vital role in the patient's future adjustment.



## PSYCHOPATHOLOGY IN RHINOPLASTY

Surgeons are often faced with the problem of overcoming a patient's objections to an operation that is definitely indicated. The motivating forces behind the reverse of this situation, when the patient *insistently demands* operation, are complex and often deeply rooted in unconscious drives and defenses. In those individuals who seek nasal plastic surgery for apparent social, economic or racial reasons, as in the case of public entertainers who have to measure up to conventional standards of beauty, there are presumably deeper psychodynamic forces which prompt the decision for operation. These factors have recently been analyzed in a comprehensive paper by Linn and Goldman. (10)

The nose occupies a unique position in the psychic representation of bodily structures. It is a conspicuous, unpaired midline organ which may assume the unconscious emotional significance of a phallus through the mechanism of displacement. Its size and proportions may be characteristically masculine or feminine especially after adolescence. In effect, it is an organ with secondary sexual characteristics. The following case history illustrates how a deep seated masturbatory homosexual conflict may express itself through an obsessional preoccupation with the nose and lead to an insistent demand for plastic surgery.

At the age of 18, R. A. S. had an emergency appendectomy performed following which he developed symptoms of an obsessive-compulsive neurosis. This took the form of almost constant preoccupation with his facial appearance especially the size and shape of his nose. He frequently manipulated this organ into various positions while examining it in a three-way mirror. When alone he would improvise an arrangement of mirrors whereby he could examine the minute details of his profile. He smuggled food into his room so that he could observe the movements of his jaw and face while chewing. As these practices continued, he grew increasingly tense and excited and proportionately more secretive. He began to compare his nose and chin with those of other men and later with those of women. "I became obsessed with thoughts about my nose, was it correct for my face? was it too large? was it even or was one side of the bridge higher than the other? I secretly had profile pictures taken in those 25 cent photo booths; they were awful and scared me even more. Then I told my mother about it and she tried to talk me out of it; we talked more and more and after a while I would cry and she'd cry and soon we were both hysterical. One day I had a terrifically bad mood and was frightened, I felt as if I would kill myself". The patient subsequently consulted a number of plastic surgeons who all felt that rhinoplasty was not indicated but with persistence he finally found one who agreed "to take the potato off the end of my nose". He then became enmeshed in distressing doubts and indecisions. "I debated it several weeks, growing more hysterical; mother consented if I wanted it. I walked the streets in panic, unable to decide, afraid if I would look strange after the operation". After exhausting himself with this painful ambivalence, the operation was finally performed. Following the procedure he was both euphoric and anxious. He feared that his friends might notice the alteration and was greatly relieved when it passed unnoticed. Shortly thereafter he began to wonder whether his nose looked better before its repair and he expressed the wish that it be restored



to its original form. His nasal obsessions persisted until his masturbatory and homosexual problems were analyzed. It is noteworthy that he was pleased with the large size of his penis while feeling that his nose was too long. Further, when he masturbated he had homosexual fantasies and did so in front of mirrors placed at such an angle that he could only see the penis and not the remainder of his body and would then imagine that it belonged to another man. Whenever the opportunity presented itself as in the dressing lockers of swimming pools he had a similar need to compare his genitals with those of others. The removal of the appendix was the incident that mobilized his castration anxiety and led to the displacement upwards to the nose as a substitute genital, thus unconsciously defending himself against injury to the treasured phallus.

#### DELIRIUM

Delirious states, especially in the early stages, are frequently overlooked on a surgical service. Their early recognition and prompt control are essential lest the patient become unmanageable and require transfer to a psychiatric division.

Delirium is a symptom-complex characterized by clouding of consciousness with disorientation, fear and the presence of hallucinations and delusions. The reaction is ushered in by restlessness, irritability, apprehension, sensitivity to noises and bright lights, insomnia and disturbing dreams. The patient is often distractible and slow to grasp the meaning of what is being said or of changes in his immediate environment. As the illness progresses, the symptoms are accentuated at night with illusions, hypnagogic hallucinations and temporary disorientation upon awakening. Gross disorientation for time, place and individual recognition finally appear and with it fear verging on panic, hallucinations (usually visual) and delusions of persecution or impending danger. The latter have particular clinical significance as the patient may injure himself or even commit suicide in a confused and bewildered attempt to escape from distorted sensory impressions and imagined enemies.

E. R. a 70 year old white unemployed male was referred to the surgical service because his local physician found a large abdominal mass. The patient's sole complaint was insomnia of 2 months duration, and there were no gastro-intestinal symptoms or alterations in bowel function. On examination his nutrition was maintained, the heart and lungs disclosed no abnormality and the blood pressure was 148 systolic, 98 diastolic. A large, firm, movable, non-tender mass that moved with respiration extended from below the umbilicus to the xiphoid. The prostate was moderately enlarged. Complete blood studies were normal. A barium meal examination disclosed no abnormality in the esophagus, stomach or duodenum. On fluoroscopy, however, there was a suggestion that the mass produced pressure on several loops of small bowel. A barium enema examination was unsatisfactory due to poor cooperation. Psychiatric study disclosed gross errors in orientation, poor retention of recent events, intense fear and visual hallucinations. He did not know the name of the month and insisted that he was born in 1975. During the examination he lapsed into German but when urged to speak English he did so in a mumbling, indistinct manner. He repeatedly failed

to recall the physician's name after a 3 minute interval although he was able to repeat it promptly when asked to do so. He thought he had been in the hospital for 2 or 3 weeks whereas it was actually but 7 days. He was particularly disturbed and apprehensive at night; he constantly called for the nurses shouting that a man was dying. He once complained that fish were swimming about him. Delusions were prominent and he insisted that everyone was laughing at him; he interpreted attempts to take his rectal temperature as a sexual assault. He often talked incoherently with repetitiousness and great circumstantial detail. His sleep was restless with frightening nightmares; he frequently left his bed and wandered about the ward. In view of his psychiatric status which precluded any cooperation and the possibility of a more severe post-operative reaction, exploration was deferred.

In the management of delirious states, rest, adequate nutrition with vitamin supplements and the avoidance of sedatives that tend to increase toxic reactions are of great importance. Paraldehyde in large doses to insure sleep is usually the medication of choice. It is essential that the patient's strength be conserved and exhaustion prevented. Constant reassurance and painstaking explanations of all procedures will tend to lessen fear and resistance to examinations. A delirious patient should never be left alone, the surroundings should be quiet and dangerous objects removed. Whenever feasible, he should be attended by the same nurse to prevent added confusion. It may be desirable to keep a light in the room until he falls asleep, thus minimizing the misinterpretation of shadows and other environmental details (11).

#### REACTIVE DEPRESSION

Depressions as reactions to circumscribed and distressing life situations are not infrequently seen after operations, especially when they interfere with the exercise of emotionally charged functions such as the procreative, etc. These affective states are accompanied by physiologic changes involving many systems and may lead to anorexia, weight loss, constipation, insomnia, menstrual irregularities, decreased sexual drive, alterations in muscle and skin tone and retarded motor activity. When anxiety supervenes and leads to agitation, these functional changes are so modified that the patient may become restless and hyperactive. Such hyperkinesis may also be viscerally reflected in the form of hyperperistalsis which may result in diarrhea. Patients who appear totally disinterested in their surroundings may still be acutely aware of what is transpiring. They will often brood over casual comments weaving them into the structure of their depressed state and may become so disturbed that suicide may be attempted. Such reactive depressions are of shorter duration than those in which a constitutional predisposition plays the significant role and are therefore more amenable to psychotherapy.

S. K. a 62 year old married waiter was admitted to the Mount Sinai Hospital in October 1946 complaining of anorexia, fatigue and a 40 pound weight loss of 1 year's duration. Watery diarrhea made its appearance 2 weeks prior to admission. In April 1945 he had a suprapubic prostatectomy and soon after be-

came concerned about the loss of potency. He then noted weakness, occasional headaches, anorexia and insomnia. Constipation, which had been life-long became accentuated and required constant catharsis. Gastro-intestinal roentgenograms were always negative but despite this he was advised to enter the hospital for further study. He responded with extreme tension and anxiety to this suggestion and experienced mild abdominal cramps with loose, watery stools. On examination he was pale and emaciated. He sat alone for long periods staring into space, spoke slowly and in monosyllables. The peripheral vessels were firm and the fundi disclosed grade II arteriosclerosis. The heart was slightly enlarged and the blood pressure 170 systolic, 110 diastolic. The hemoglobin was 79 per cent, there was no occult blood in the stool and sigmoidoscopy was negative. A barium enema examination was inconclusive but disclosed a short constricting filling defect in the sigmoid which was believed to be due to extrinsic pressure. His depression progressively increased during these time consuming investigations. He confided to the psychiatrist that he had overheard considerable discussion on ward rounds of "neoplasms and mitotic figures" which he soon discovered signified cancer; his anxiety became extreme and he had suicidal ideas. Exploration was finally performed and revealed only a markedly redundant and freely movable sigmoid. A large left inguinal hernia was repaired from within by excising the redundant peritoneum. With patient, sympathetic explanation and reassurance he showed some measure of improvement and on discharge was less depressed.

It is apparent that alterations in bowel function were profoundly affected by his emotional state. The psychologic significance of his earlier operation did not receive sufficient attention in evaluating the clinical picture. The exploratory procedure was definitely indicated but the patient could well have been spared some of his suffering through an adequate formulation at a level that he could grasp. Discussions and comments overheard at the bedside may have a devastating affect on the patient's morale and his future behavior. Physicians are inclined to minimize the patient's fund of information, often gleaned from diverse sources. Serious consideration should be given to establishing changes in the current practice of bedside teaching and rounds so that patients may be adequately protected from emotionally disturbing comments.

#### THE SURGICAL DEVOTEE

The surgeon is confronted with an especially trying problem when indications for operation are not sharply defined and the patient nevertheless insists on surgical intervention. In the following case, the immediate psychodynamic factors involved were elicited in a few interviews. An evaluation of the entire clinical picture, however, led the psychiatrist to agree to the need for operation, although the patient's insistence was a manifestation of a severe psychiatric illness.

L. B. a 33 year old divorced woman was referred to the psychiatrist because of her insistence on the removal of her rectum and sigmoid. A transverse colostomy for the control of a severe ulcerative colitis had been performed 2 years prior to this investigation. The colostomy had functioned well but she recently

had experienced a return of a fistula in the right buttock as well as severe abdominal cramps. She was quite positive in her insistence that the excision of the rectum and sigmoid would bring her complete relief.

At the time of her first admission to the Mount Sinai Hospital, in October 1938, a history of temporary complete blindness due to interstitial keratitis of luetic origin at the age of 11, was obtained. She was then hospitalized for a space of 6 months and following intensive bismuth and arsenical therapy the ocular symptoms gradually receded. In 1936, at 21, she had rectal pain on moving her bowels and small amounts of blood were seen in the stool. The presence of hemorrhoids was determined and both pain and bleeding subsided with the use of suppositories. In the following year, following 6 arsenic and bismuth injections, she had severe diarrhea with as many as 10 loose movements a day; this soon subsided when the medication was withheld and a diagnosis of acute arsenical poisoning was established at a city hospital. Following 6 months of complete freedom from diarrhea or pain, she was married in September 1938. One month after marriage, cramps and diarrhea recurred. She then described her husband as a "sex maniac" who brutally attacked and forced her to submit to passive pederasty. Following the first such experience she bled for 3 weeks. She attempted to leave him but he threatened suicide unless she remained. She was then admitted to the hospital where she passed as much as 6 ounces of blood per rectum several times daily. Sigmoidoscopy revealed ulceration of the rectum and sigmoid. Following discharge from the hospital she lived with her mother for 14 months, much of the time in bed. Her mother, knowing nothing of her sexual experiences, finally succeeded in effecting a reconciliation and the patient returned to her husband. Soon thereafter he again forced her into anal coitus with prompt return of the diarrhea, weight loss and pains in the area of the right hip. A short time later, her mother became ill with a cerebral ailment, presumably general paresis, and the patient promptly became worse. Early in 1941 a fistula appeared near the painful area in the hip and soon 3 more fistulae developed over the right buttock. In an effort to control the diarrhea she received opium over a 3 year period which gradually led to addiction. When the drug was withheld, she complained of generalized abdominal cramps, weakness and vertigo. She had an acute exacerbation of her symptoms in 1943 when her mother died but she did not seek re-admission to the hospital until May 1944 when the presence of a chronic non-specific ulcerative colitis was established. Barium enema examinations did not show any evidence of disease above the rectum. Because of the recurrent fistulae, progressive deterioration in her physical status and repeated rectal bleeding, a transverse colostomy was performed. At operation, the sigmoid appeared slightly thickened and several lymph nodes which were removed for study, did not show any significant changes. Following the procedure, the colostomy functioned well and the fistulae gradually closed. The consumption of morphine was reduced and she gained weight. At the time of discharge, she had decided to divorce her husband.

It should be stressed that she took great pride in maintaining her colostomy in good condition and was able to take an enema each morning without further drainage for the remainder of the day. In October 1946 she became attached to



a man who soon suggested marriage. She simultaneously experienced a recurrence of abdominal cramps and the fistulae over the right buttock re-opened. A bloody, mucous discharge from the rectum soon appeared and she entered the hospital for the third time in March 1947, insisting that the rectum be completely removed. During the interview she was highly disturbed, wept profusely and again expressed the fear that she might be subjected to an anal attack; she nevertheless rationalized her desire for rectal resection on the basis of the recurrent fistulae. The operation was performed in April 1947 and was followed by an uneventful recovery. The resected rectum and sigmoid disclosed a chronic non-specific ulcerative colitis. She continued to manifest considerable pride in her colostomy and was pleased that it served its purpose so admirably with but little inconvenience. On one occasion, when another patient with carcinoma of the rectum expressed dread of a permanent colostomy, she volunteered to convince her of its advantages and effectively demonstrated how she cared for her own. The patient was asymptomatic until February 1950 when she was readmitted for a stricture of the colostomy which was easily revised by freeing the underlying fascia which had formed a constricting band around the bowel.

It is beyond the scope of this paper to analyze the factors involved in the evolution of this woman's ulcerative colitis. The relationship between the recurrent attacks of colitis and the threat of anal intercourse which presented itself as an insoluble life situation is, however, apparent. Her insistence on operation was a means of insuring herself against the dreaded anal attack and enabled her to obtain whatever anal erotic gratification she may have unconsciously desired through the displacement of her interest to the colostomy.

#### SURGERY IN PSYCHOTIC PATIENTS

The patient with a recognized psychiatric illness who requires surgical intervention poses a difficult problem for the surgeon. The need to evaluate the role played by psychologic factors in the causation of symptoms and the possibility of precipitating an acute psychotic crisis must always be recognized. Under such circumstances pre-operative psychiatric treatment will aid in determining the optimum time for intervention and minimize emotional complications. In the following case the liaison psychiatrist, aware of this danger, recommended close observation and adequate psychologic preparation for the procedure.

C. D. a 37 year old unmarried woman was admitted to the Surgical Service in November 1949 because of an exacerbation of long standing rectal pain following her mother's death. Examination disclosed an anal ulcer and a retroverted uterus. Roentgen studies of the colon were negative. The history strongly suggested a factitious element probably due either to instrumentation or anal masturbation. She had nursed her father through a prolonged illness 20 years earlier; he had had considerable rectal bleeding and finally succumbed to a rectal carcinoma. Two years later she had slight rectal bleeding which she interpreted as due to a "scratch on the anus". A severe cancerphobia was soon manifested; she frequently resorted to suppositories, even using her fingers to assist stool evacuation. She became depressed, anxious and expressed the fear of "going crazy". Many bizarre and confused ideas relative to anal birth and rectal men-

stration led the surgeons to defer operation, whereupon she left the hospital against advice. She grew more depressed, contemplated suicide and her pains were proportionately worse. She was admitted to the Psychiatric Service on January 1950 where she was believed to have a schizophrenic psychosis with malignant hypochondriasis. Her sexual fantasies indicated rectovaginal confusion with coitus likened to a violent mutilation of both organs. Her fantasies about the operation were that the "rectum would be turned inside out, flesh would be cut out and then the fun begins". She reasoned that if she became pregnant, the tip of the uterus would rise into the abdomen and relieve pressure on the rectum and spine thus effecting a cure.

Treatment was directed to the encouragement of a supportive relationship with emphasis on reassurance, explanation and education. Her fantasies were repeatedly subjected to the test of reality especially when there was danger of her acting them out as in the case of her "reasoned" cure through pregnancy. Deeper interpretation beyond the more superficial was avoided. With this approach she finally consented to excision of the anal ulcer, tolerated the procedure without difficulty and the pain was soon relieved. She is now able to work, support herself and appears to be making a fairly adequate social adjustment despite the seriousness of her mental illness.

#### COMMENT

Several examples of commonly observed emotional disturbances related to surgery are analyzed. In each instance the prospect of operation played a critical role in the patient's behavior. Emotional responses to the operative stress may be varied and bizarre and are found to be linked with specific situational factors, deeply rooted in psychologic conflicts which can, in most cases, be traced to childhood experiences. The more immediate social and cultural influences may similarly initiate the so-called "irrational" reaction whose form and content are determined by earlier responses to stress. Separated from home and family, the patient is confronted with restraints and restrictions which induce a sense of helplessness, frustration and fear. Furthermore the dread of anesthesia with its attendant loss of conscious control and the impending operation are all ominous threats which serve to facilitate regression to childlike behavior. When the individual's previous experiences include operation, bodily injuries, parental death or separation or disturbances in psychosexual development, there is a greater likelihood of reactivation of earlier emotional patterns in the face of operation. The recognition and management of such mechanisms through modern psychoanalytic and psychotherapeutic techniques have aided in resolving many problems which hinder recovery.

It must be recognized that progress in the management of the surgical patient's emotional needs has not kept pace with the almost bewildering advances in operative techniques, biochemical and nutritional control and the use of antibiotics. The very complexity of these measures subjects the surgeon to a tempo which permits him little opportunity to acquaint himself with the patient's personality and his problems.

Our studies have emphasized the crucial need for the early recognition of the

surgical patient's emotional disturbances, lest permanent psychological invalidism ensue. We believe that the great majority of the surgical patient's psychologic hazards may be effectively controlled through the simplicity of the traditional and superficial techniques of sympathy, explanation, interpretation and reassurance. The authoritarian figure of the surgeon can, in many instances, succeed in dispelling states of demoralizing anxiety through a kindly, understanding manner and a few words of comfort. A similar approach by the surgeon's assistants and other members of the staff will further assuage much of the surgical candidate's fear.

At the Mount Sinai Hospital a group of liaison psychiatrists are attached to the surgical services. They act as consultants in all suspected emotional problems. Not the least of their functions, however, is the encouragement of a psychiatric orientation in the surgical personnel. Their mere physical presence seems to act as a stimulus and a much closer integration has thus been effected. The psychiatrists attend all major rounds, freely discuss joint problems, and experience would indicate that the surgeons fully recognize their important contribution to comprehensive management. Should the emotional disturbance be of some severity, more intensive psychiatric investigations are instituted either on the surgical ward or the patient is transferred to the psychiatric division. In certain elective procedures, operative intervention is at times deferred at the psychiatrist's request. A few patients will require deeper psychologic study and are then referred either to the out-patient department or to private psychiatrists.

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# FETAL DEFECTS RESULTING FROM VIRAL DISEASE OF THE PREGNANT MOTHER\*

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The current interest in the effects on the fetus of viral disease in the pregnant mother was initiated by the publication in 1941 of the observations of N. M. Gregg, an Australian ophthalmologist, who called attention to the appearance of fetal malformations in infants born of mothers who had acquired rubella in the early months of pregnancy. Gregg's findings stimulated considerable discussion; many cases were reported, especially in the United States and the whole study of fetal malformation received tremendous impetus. Whereas we had been previously taught that fetal malformations were due to disturbances in the original germ plasm, it became evident that deleterious influences acting as late as the third month of gestation were able to influence the orderly development of the fetus and result in congenital malformations. Some of the more significant work on this subject was done by Joseph Warkany who particularly studied the effect on the offspring of deficient maternal diets. He classifies fetal defects as follows:

A) Defects in the genes;

B) Adverse conditions affecting the developing ovum, (a) actinic, (b) dietetic, (c) infectious.

In studying pregnant rats he was able to produce a characteristic type of fetal deformity when he deprived the mother of certain dietary factors. For example, animals deprived of vitamin A had pups with defective eyes, a retrolenticular membrane replacing the vitreous. Riboflavin deprivation in the mother led to certain skeletal defects in the offspring and vitamin D deprivation also resulted in specific abnormal development. Warkany lays special stress on the fact that the same deformity may appear as the result of varied causes. Thus cleft palate may be due to a genetic aberration, i.e. a particular strain of mice may regularly show this defect or it may appear after exposure of the pregnant mother to the effects of x-rays, or in the young of mothers who have been placed on a riboflavin-free diet during pregnancy. Another illustration is provided by microcephaly which may be familial (genetic), may follow toxoplasmosis, or be due to exposure of the mother to roentgen rays in the second or third month of pregnancy.

The fact that we now know that rubella, a disease caused by a virus, can result in fetal malformation, has led to much speculation as to the effect of other viruses on the offspring and it is of interest to consider how differently viruses act on the tissues of young in contrast to adult organisms. Many investigations have been carried on along these lines. For example it was shown by Olitsky that the virus of vesicular stomatitis or of equine encephalitis could be cultivated in the chick

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embryo but that the 4 day old chick was completely resistant to it. Similarly, Sabin has reported on the varied resistance offered to viruses by young and adult animals. Very young mice when injected with certain viruses develop encephalitis, whereas, adult mice do not. It has been shown that these viruses are neurotropic and that in the young animal they travel along a nerve to the central nervous system, in adults on the other hand a block develops in the nerve and prevents the virus from reaching the brain thus producing encephalitis. However, if the virus is injected directly into the adult brain, encephalitis results. Further, if the virus is injected intraperitoneally, the young mouse develops encephalitis but the adult fails to do so. It is of interest to compare this with the action of the rubella virus which also acts so differently on the mother and the fetus.

Of special note is a report of an investigation published in 1947 by Hamburger and Habel. By the inoculation of the developing hen's egg with the virus of Influenza A, these authors were able to produce "a specific pattern of localized malformations"—in other words, a group of varied defects which appeared quite regularly in the injected embryo. Hamburger and Habel's conclusions are as follows:

"Experimental evidence has been presented to show that Influenza A virus (PRS) has teratogenetic effects on the early chick embryo. It produces a specific syndrome, comprising microcephaly and micrencephaly, twist of the axis, and impairment of growth of amnion. Furthermore, the virus is lethal for early embryos within 3 days after infection. The mumps virus is also lethal for early embryos within 5 days after infection. It does not produce specific abnormalities but seems to raise the incidence of malformations of the types which occur occasionally in uninfected chick embryos. These results place Influenza A virus in line with rubella virus as a teratogenetic agent. Furthermore, our observations on Influenza A infections in chick embryos confirm the observations on rubella in humans in that only infections of early embryos result in abnormalities. Chick embryos of 4 days' incubation are killed by the influenza virus, but it seems that at this stage of development most organs have passed the critical period at which their morphogenesis can be directed into atypical channels. In this respect, it is of interest to find that the patterns of infectiousness are different for the embryo and for the fully developed structures. In the embryo, the brain-tissues seem to be particularly susceptible to Influenza A virus, whereas in the adult the respiratory mucous membranes are primarily affected. In mumps, the inflammation of the salivary glands is frequently combined with meningitis, but no effect on the brain was found macroscopically in embryos. The situation is the same as in rubella where the embryonic defects seem to have no obvious relations to the manifestations of rubella infections in older phases of life."

More recently a series of experiments on rats by Gillman, Gilbert, Gillman and Spence has thrown more light on the occurrence of congenital defects and I think it worth while to quote a portion of an Editorial from the Journal of the American Medical Association (October 30, 1948) where their work has been very well summarized:

"Recent experiments reported by Gillman, Gilbert, Gillman and Spence should

shed new light on the many unknown physiologic factors which bear on the problem of congenital anomalies. Believing that later effects of chronic malnutrition were causally related to a metabolic disorder induced by entry of abnormal particles into and by qualitative changes in plasma proteins, these investigators treated female rats with trypan blue because of its plasma albumin-binding properties. A random group of 100 breeding female rats and 25 male rats on normal stock diet were given repeated injections of 1 cc. of trypan blue at fourteen day intervals. Of the 100 females, 11 remained sterile. In a total of 697 offspring born in 118 litters, 19.2 per cent presented gross macroscopic malformations detectable at birth. Malformations such as hydrocephalus, spina bifida, tail defects, eye defects and defects of other systems ranged in decreasing numbers, averaging 1.4 anomalies per rat. Timing of dye injection was extremely significant. In female rats that received injections before conception as well as one additional injection during pregnancy, incidence of abnormal pups was 25 per cent. Mother rats given injections the seventh day of pregnancy had an 80 per cent incidence of abnormal pups. Rats receiving only one injection on the day before conception showed a 25 per cent incidence of abnormal pups. Rats receiving one injection, on the sixteenth day before conception, gave birth to pups in which jaundice developed within the first three days of life. Among all offspring, high neonatal mortality, reduction in size of litters, low birth weights and a general retardation of postnatal development occurred.

The authors express the belief that the original hypothesis which prompted them to use trypan blue for producing congenital malformations proved efficient. The metabolic effect was operative when rats were fed a balanced diet. Trypan blue was bound to plasma albumin, and the use of the dye could be appropriately manipulated to increase the incidence of malformed offspring to 80 per cent. The authors cite what they consider to be an apparent parallel in the development of congenital defects in offspring of trypan blue-treated rats and defects in infants following maternal rubella infection. It is suggested that the supposed mode of action of the rubella virus on the human fetus be reexamined, as passage of virus through the placental barrier is debatable and as they have demonstrated that the trypan blue in maternal rats did not enter the fetus, the amniotic epithelium or amniotic fluid. All embryonic tissues apart from the yolk sac were free from trypan blue particles.

Discoveries concerning the connection between maternal rubella infection and developmental defects in offspring plus previously known similar effects of diet restriction and irradiation in animals and the described work of Gillman and associates with trypan blue open an important new field for basic research. If, as the experiments of Gillman and associates tend to demonstrate, the effects of trypan blue and, by inference, rubella virus, are not direct effects on the fetus but cause remote preceding metabolic states which subsequently interfere with fetal development, the speculative number of viruses, bacteria and chemicals which may produce such metabolic effects are legion. Additionally, the reported occurrence of congenital deformities from preconception effects of rubella infection and trypan blue definitely reduce the nature-nurture or heredity-environment argument regarding developmental influences to the preconcep-

tion period, wherein affective metabolic states in the male must also be properly considered. While this does not diminish the absolute importance of gene influences, it most certainly increases the relative importance and scope of environmental factors to be considered in human development."

With these facts in mind, let us consider some of the viral diseases which may pass from the mother to the fetus. Among these are rubella, varicella, smallpox, measles and certain forms of encephalitis. Chicken pox has repeatedly been described in the infant during the first few days of life where the mother has just recovered from the disease. Smallpox may be transmitted to the fetus and may cause abortion in 50-60 per cent of cases. Béla Schick has called attention to an extremely interesting fact concerning smallpox. Over 40 cases are known where an immune mother who has had smallpox earlier in life is exposed to the disease while pregnant. Her offspring acquires the disease *in utero*. Schick explains this on the ground that the mother's immunity is cellular rather than humoral and that the antibodies are unable to be transmitted to the fetus. In countries where there is smallpox, pregnant women know that they should avoid contact with cases even though they themselves are immune. In this connection it is interesting to note that vaccination of the pregnant mother is apparently harmless for the fetus. Bellows, Hyman and Merritt made a careful statistical study of this, when 5,000,000 persons were vaccinated against smallpox in New York City in 1947. There were no more fetal defects in the women vaccinated during early pregnancy than in controls and it was shown that smallpox vaccination during pregnancy does not increase the incidence of congenital malformations, stillbirths, abortions or infant deaths.

Infants of mothers ill with measles have been reported as born with the disease. I saw a newborn infant develop the disease on the 7th day of life, the mother having just recovered from the illness. Recently 2 cases have been reported by Hagströmer where immune mothers were exposed to measles during their first month of pregnancy. Both pregnancies resulted in deformed offspring, one infant had a cleft palate, the other a cleft palate, micrognathia and a rudimentary ear. Such cases may of course be merely coincidences, but their occurrence should be reported. Maternal influenza may result in a dead fetus in which typical lesions of influenza may be found. Rabies has been inoculated into dogs from the brain of a fetus whose mother had died of the disease. The injected animals developed rabies.

Lymphocytic choriomeningitis has been shown to pass from mother to offspring in mice, and the virus has been recovered from the fetal brain. Poliomyelitis on the other hand does not seem to affect the fetus. Hoyne reported an interesting experiment: a pregnant woman had bulbar poliomyelitis and the fetus died of asphyxia. The fetal spinal cord was inoculated into monkeys but no virus could be demonstrated. Most authors agree that since the virus of poliomyelitis is not present in the blood stream, there is no way that it can pass through the placenta and attack the fetus.

It is quite certain that viruses may pass through the placenta and affect the offspring. The examples just cited leave no doubt about this; in fact the fetus



may even be affected by exposure to a viral disease to which the mother is immune. When we consider the frequency of fetal damage from maternal virus infection, it is significant that there are very few authentic instances of such damage except in the case of rubella. In the special report of the Academy of Pediatrics on this subject, only 13 such cases were reported. Of 13 cases of maternal measles during the first 4 months of pregnancy, 4 were followed by defective offspring; of 19 cases of mumps, 3 were followed by defective offspring; of 4 cases of chickenpox, 1 was followed by an infant with cataract; of 5 cases of infectious mononucleosis, 3 were followed by defective offspring. It is noteworthy that the number is altogether too small to draw any definite conclusions and that in this group of cases, infectious mononucleosis is the one illness where the percentage of defective infants is significant, but we must not lose sight of the fact that we are only considering 5 cases.

Let us now turn to a consideration of rubella, the disease which initiated so many discussions and investigations on this subject. When Gregg's paper appeared in 1941, physicians were amazed that a disease previously considered so mild should produce such devastating effects in the fetus. There was much discussion as to whether the disease affecting the mother was really rubella or whether some new type of infection had suddenly made its appearance. However it soon became evident that the disease was actually rubella and case reports appeared in England and in many parts of the United States citing instances in which women acquired the disease in the early months of pregnancy and gave birth to defective infants.

In describing the first cases of fetal defects in Australia, it was pointed out that the maternal illness was quite severe, that there was often sore throat, marked swelling of the cervical nodes and painful joints. As there was a concurrent epidemic of sore throat in Australia, there was discussion as to whether this might also be involved in the etiology of the syndrome. Another theory was that rubella had suddenly assumed new virulence which resulted in effects previously not encountered. Quite recently Beswick, Warner and Warkany have discussed this question and have reported a number of pertinent cases which help to show that the rubella present in 1940 in Australia was not necessarily more virulent than the disease as we know it. They pointed out that in Cincinnati they were first acquainted with the post-rubella syndrome in 1943 and that they had been informed of several cases occurring in Texas at the same time. Incidentally I may add that I saw what I believe to be the first case diagnosed in New York City, an infant with congenital cardiac disease and bilateral cataract. This was reported by the ophthalmologist, Dr. A. Reese who operated on it. Within a very short time I saw a second newborn infant with the same anomalies where the mother also gave a history of rubella in early pregnancy. I then recalled an infant whom I had seen in 1941, who was born in New York but was conceived in London in 1940. This baby was also operated on in New York after which the family moved to London. On communicating with the mother I then obtained the history that she had had undoubted rubella in early pregnancy in London when the disease was epidemic. In other words, rubella in England caused the



same fetal malformations as rubella in Australia. Incidentally this infant had not only bilateral cataracts, but also cardiac malformation, deafness and mental retardation. The mother has since had two normal children.

To return to the report of the Cincinnati investigators, they record a pair of twins of unlike sex who had bilateral cataracts, congenital heart disease, deafness, microphthalmia and mental retardation, followed by epilepsy and glaucoma; the mother had had rubella during the third week of pregnancy in the United States in 1930. You will note that these infants were born a decade before the Australian cases. They also report another case of deafness, mental retardation, athetosis and epilepsy in a girl whose mother had rubella in the sixth week of pregnancy acquired during an epidemic in 1936.

As these authors show, there are many reasons why the relationship between rubella and fetal defects should have gone undetected for so many years. We have pointed out that various noxious agents acting on the pregnant female may give rise to the same defects in the offspring. Warkany and his coworkers report 2 cases of the rubella syndrome in infants whose mothers gave no histories of any illness nor known exposure to rubella during their pregnancy. They also mention 3 instances of fetal defects where the mothers were definitely exposed to rubella in early pregnancy without any noticeable rash. They may possibly have suffered from rubella in a sub-clinical form. The Cincinnati authors' conclusions are of interest; they say, "The fact that maternal rubella causes a great variety of anomalies which are not specific for this etiologic factor explains why an occasional observer could not draw the conclusions reached by Gregg who saw the results of an epidemic in which an unusual number of adults were affected. The occurrence of the "prenatal rubella syndrome" in children whose mothers do not give a history of having had rubella in early pregnancy contributes to the confusion of the occasional observer. The discovery of rubella as a cause of congenital anomalies was made possible through the correct interpretation of a natural experiment by a mind which was 'prepared for it.' "

I reviewed the subject of rubella in 1946 before the American Academy of Pediatrics meeting in New York City and was able to collect about 200 cases of defective infants including some under my own observation. Since then many more cases have been published so that in 1949 Wesselhoef reported 656 cases, though there may have been some duplications.

Maternal rubella may be followed by abortion, stillbirth, a deformed infant, or finally, a normal infant. Wesselhoef has noted 31 cases of abortion in women who had rubella during pregnancy. Twenty seven of these occurred during the first 4 months of pregnancy. I can add one more, a woman who had rubella definitely diagnosed in the first few weeks of pregnancy followed by the removal of a macerated fetus at 6 months. She subsequently gave birth to several healthy children.

If the infant is carried to term, it may be born with one or more defects. In their order of frequency these appear to be eye defects, heart lesions, deafness with mutism and microcephalus. Many of the children grow up mentally defective. Many suffer from more than one defect. As a matter of fact, in most

cases the defects are multiple and we may speak of "the rubella syndrome" in which the child is afflicted with cataract, heart malformation and mental retardation. You may recall the repeated experimental production of a group of characteristic defects in the developing hen's egg by infection with influenza A virus. The ocular lesion is usually a cataract but microphthalmia, buphthalmos and congenital glaucoma also occur. The cardiac lesion is most often a patent septal defect.

One of the most perplexing and as yet unsolved questions concerning the rubella problem is one dealing with the regularity with which fetal defects follow maternal disease. There is no longer any doubt that rubella is the cause of fetal malformations but there is no unanimity of opinion as to the frequency of their occurrence. It is agreed by all observers that the earlier in pregnancy the mother is taken ill the greater is the chance that the infant will be defective and the first trimester is the most dangerous period. There are reported instances of defects following rubella occurring later in pregnancy but the chance of transmission is certainly greatly diminished at this time. I have under my care 2 perfectly normal infants whose mothers undoubtedly had rubella in their fourth month of pregnancy.

Of great interest is the fact that there are several case reports where the mother contracted rubella before conception and the ensuing pregnancy resulted in a defective offspring. Wesselhoeft mentions one case of a woman who had rubella 6 weeks before conception and bore a child with congenital cardiac disease, bilateral cataracts and complete deaf mutism, and a second case of rubella 10 days before conception which resulted in a child with patent ductus, bilateral cataracts and hydrocephalus. These instances are of particular interest in connection with the experiments with trypan blue already referred to where injection of the dye before conception resulted in fetal malformation.

This question is of major importance to practitioners since every pregnant woman who has rubella invariably wants to know what her chances are of having a normal child. When Gregg and Swan published their papers, they concluded that if the maternal infection occurred in the first 6 weeks, the percentage of defective offspring might be almost 100 per cent and in the first trimester at least 50 per cent. It was soon realized that these data were obtained by collecting and tabulating the large numbers of observed defective infants; however, the important question of the frequency of occurrence of normal infants after maternal rubella could not be settled in this manner.

A committee appointed by the National Association for the Prevention of Blindness and the American Academy of Pediatrics has published a report on results obtained by a questionnaire sent to 6000 physicians in the United States including only those listed as members of the specialty boards of Obstetrics and Gynecology, Ophthalmology, Otolaryngology and Pediatrics. They also sent an abbreviated questionnaire to every physician in the state of Kansas. Their findings brought out the significant fact that rubella often appears in epidemic form in various parts of the United States in the spring of the year and that the majority of the defective infants are born in the fall thus showing a definite

relation between the acquisition of the disease and fetal damage. They report on 199 mothers who had rubella in pregnancy with 32 normal infants and 167 with defects. They again emphasize the great difficulty in evaluating the true percentage of defective offspring. A mother is more likely to recall an illness in pregnancy if she has a defective offspring. Rubella is often so mild that it may be almost unnoticed and quickly forgotten, especially if pregnancy results in the birth of a normal child. In an analysis of statistics it appears that about 5 per cent of congenital anomalies may be attributed to maternal rubella.

Since congenital deaf-mutism is one of the commonest manifestations of the rubella syndrome, otologists have attempted to investigate the frequency of its occurrence. A good example of this is the work of Clayton-Jones who investigated the etiology of deafness in some of the schools for the deaf in England. Of 18 deaf children in one school, a history of maternal rubella was obtained in 8; a ninth was probable and a tenth was possible. In all the positive cases the disease occurred in the first 4 months of pregnancy. Jones observed that the affected children were all born between August 24, and October 26, 1940 whereas the birthdays of the remaining children were scattered between 1929 and 1941. In 3 other schools for the deaf 8.9 per cent of the affected children were born of mothers who had had rubella during pregnancy. The 1940 epidemic of rubella in England seems to have attacked an unusually large number of young adults which may account for the numerous cases of fetal involvement.

In this country, Conte, McCammon, and Christie also surveyed congenital anomalies and noted maternal rubella in 4.2 per cent, a figure which exceeds by at least 10 times the actual case rate of maternal rubella for the child-bearing age group in the population at large.

Fox and Bortin analyzed 2200 cases of rubella in Milwaukee in the years 1942, 1943, and 1944. They interviewed 152 women of whom 11 were pregnant when they had rubella; only one had a defective baby. In other words, there was a 9.09 per cent of defective children and they felt that this did not justify termination of the pregnancy. How complicated this whole subject is, is well illustrated by one of their cases: A woman having rubella in the second month of pregnancy gave birth to a normal child; five years previously this woman, after a normal pregnancy, had had a child with bilateral congenital cataracts. Aycock & Ingalls in Boston made a somewhat similar survey and found that about 25 per cent of women who had rubella in the first trimester gave birth to defective children.

The latest attempt to appraise the problem is a report by Chicago investigators, Abel and van Dellen, who requested information from mothers through a syndicated health column. They were asked to report on the period of pregnancy in which rubella had appeared and whether the resulting infant was healthy or not. In this series of 84 infants, 3 were stillborn, 25 were normal and 56 were abnormal. Eighty-seven per cent of the babies born of mothers who had rubella during the first trimester were abnormal as were 42 per cent of those born in the second trimester. The errors in their method are discussed by the authors and all they are willing to admit is that there is a high correlation between maternal rubella and fetal defects.



The only method by which a true evaluation of this problem can be obtained is by a collection of statistics in large obstetrical hospitals over a period of many years, where the prenatal histories can be accurately obtained, the mother observed during pregnancy and the offspring carefully examined.

Whatever the exact percentage of defective infants, the whole subject of maternal rubella is so widely known among the laity that physicians should reach an agreement as to the management of such cases. The fear of giving birth to a defective child gives rise to severe emotional disturbances in the mother and many of us have been placed in the difficult position of deciding what advice to give. Since one attack of rubella is supposed to protect against a recurrence, it would seem logical to expose girls and young women to the disease whenever it is possible as a prophylactic measure. Although such subjects may develop complications, the only one of real importance is encephalitis and this is so rare that I think the hazard is minimal.

In Australia Burnett has undertaken studies on the virus of rubella and has shown that infection of human volunteers could be induced by inhalation of atomized throat washings. He was able to infect 9 of 16 subjects. The remaining 7 failed to acquire the disease when exposed by close contact to those ill with rubella, so that it was felt that artificial transmission was fully effective in all susceptible individuals. Burnett was unable to grow the virus but found that it was present in high concentration in throat washings taken at the height of the rash. He was able to preserve it for at least 3 months at the temperature of solid carbon dioxide. When sprayed into the throats of susceptible young women, the incubation period was found to be from 13 to 20 days. Women who thus acquired rubella could transmit the disease to others by ordinary contact. It will be of interest to determine if this method of inoculation will ever come into general use.

Since gamma globulin has been found so effective against measles, it seemed desirable to try it as a prophylactic measure against rubella. A committee to study this question was appointed by the New York County Medical Society and in the fall of 1948 an excellent opportunity presented itself when an epidemic of rubella broke out in a large child caring institution in New York City; 262 children were included in this study of whom 133 were injected with 6 cc. of gamma globulin and 129 kept as controls. From the epidemiological point of view, the conditions obtaining in this institution closely simulate those occurring in the home. Controls were strictly alternated, and every other child was injected. Two cases occurred in the injected group and 2 in the controls within the first 3 days after injections were begun. It was felt that these children had become exposed too long before injection and they were therefore discarded from the series. From the fourth through the thirty-fifth day after injection, 6 children receiving gamma globulin developed frank rubella; during the same period 22 control children acquired the disease. From these figures it was believed that globulin may have been effective in preventing rubella, though it was not effective in every case. A significant observation in this series was that the older the child, the greater seemed the tendency to avoid infection, both in the control



and infected groups. No case occurred in the children between the ages of 12 and 16 years, whereas the heaviest incidence was in the 2 to 5 year age group. Perhaps different strains of the virus are prone to attack different age groups, for both the Australian and the English epidemics of 1940 seemed especially prone to attack young adults. The series in New York is of course small and the result merely suggestive. Additional work along these lines is necessary.

Many pregnant women exposed to rubella have been injected with large doses of globulin, but I know of no large series that would help determine its real value. I have records of a dozen injected women, none of whom developed the disease, and I know of two others who developed rubella in spite of injections of globulin. In this connection the following item is of interest. In the newsletter from Australia published on March 12, 1949 in the *Journal of the American Medical Association*, mention is made of the fact that gamma globulin had been prepared from the serum of convalescent rubella cases and that "This globulin has been used to prevent infection in women who have been exposed to rubella at a vulnerable stage of pregnancy. In 22 instances of proved or possible contact, serum has been administered, and in none of these cases has a rubella rash subsequently been confirmed". We do not yet know whether the prevention of symptoms in the mother has protected the fetus.

If a pregnant woman is exposed to rubella, I believe she should receive the benefit of a large dose of gamma globulin. If in spite of this she acquires the disease, termination of the pregnancy must be considered. This raises the question of abortion. In New York, as in many other states, it is illegal to perform abortion unless the health of the mother is endangered. I have discussed this with many obstetricians and the majority feel that if the woman has rubella in the first trimester and is aware of the danger to her offspring, her emotional state would warrant the emptying of the uterus. Two such cases have come to my attention. The first involved a woman who was staying with her husband at an army camp in Mississippi where rubella was epidemic. She was one month pregnant when she contracted the disease. She came north to her home in a severely disturbed mental state. Two pediatricians and 2 obstetricians agreed that an abortion should be performed. This was done and an attempt was made to study the embryo, but without success. A friend of this woman, who also acquired rubella in early pregnancy in the same camp, refused to terminate her pregnancy. After a very severe labor, she was delivered of a dead infant. On examination, the child had bilateral cataracts.

I had an interesting experience in my own practice. A mother of two children developed rubella during pregnancy. As she had a mentally defective child in an institution, the possibility of another defective child so horrified her that I sent her to a psychiatrist who concurred in my opinion that it would be extremely dangerous to permit this pregnancy to continue. She was seen by an internist and a gynecologist both of whom agreed to an abortion.

It seems a pity that the law cannot be modified so as to legalize abortion in these instances. Anyone concerned with this subject should read Wesselhoef's articles in the *New England Journal of Medicine* where he makes an eloquent

plea for a change in the present law. The birth of a defective infant who may also be blind and deaf is a frightful calamity. It is not only an unbearable burden for the parents, but the care of such a child consumes so much time and money that the normal children in the family are neglected. I have seen one woman whose first child is blind and mentally retarded as a result of maternal rubella. It is impossible to induce this woman to become pregnant again as she fears she will not be able to give the second child proper care. When one deals with such cases and witnesses the resultant tragedies, one feels the laws that permit such suffering should be changed. As Wesselhoeft puts it, "The law and medicine are subject to change in social evolution. The purpose of both is to protect and benefit mankind. Consequently, when some new development in the knowledge of medicine reveals any legal obstruction to the carrying out of a desirable preventive measure for the benefit of mankind, due consideration should be given to the enactment of modifying statutes to meet the situation."

I want to make one more suggestion, based upon a case of a young woman who recently contracted rubella. She believed that she was pregnant as her menstrual period had not appeared. She and her physician were much concerned. A week later her period appeared and it was evident that she was not pregnant. It is important to advise her not to attempt pregnancy for at least 2 months since we have seen maternal rubella even 6 weeks before conception result in defective offspring.

In this review I have attempted to inform the reader concerning the relationship of maternal virus infections to the fetus. It is a fascinating subject which opens up many new fields for laboratory and clinical investigation.

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# OBSERVATIONS ON BLOOD PRESSURE IN CHILDREN FOLLOWING AN ACUTE GLOMERULONEPHRITIS\*

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For thirty years we on the Pediatric Service have been interested in various phases of nephritis. In this communication we shall describe our observations on the blood pressure during an acute hemorrhagic glomerulonephritis in children and attempt to ascertain in their follow-up whether the subsequent blood pressure readings bear any relationship to the clinical course of primary episode.

## MATERIAL AND DEFINITION

Observations were made on 53 children seen by one of us during the acute stage of the disease. There were 32 males and 21 females, of whom 2 were colored. The youngest child was 2 years of age and oldest over 12 years. Thirty-two were under six years (60.37%), thirteen were from 6 to 10 years old (24.52%) and 8 were from 10 to 12 years of age (15.09%).

The average time of hospitalization for acute nephritis was as follows: 12 children were hospitalized for less than 1 month, 30 from 1 to 2 months, 11 from 2 to 3 months.

In agreement with previous experiences, the etiology of nephritis was usually antecedent infection. In 47 children there was a respiratory infection of the upper or lower portions of the respiratory tract; in 3 there was an antecedent scarlet fever; in 2 an impetiginous skin infection and in 1 no definite etiology could be ascertained.

At each visit to the Pediatric Follow-up Clinic a general physical examination was made which included a blood pressure reading and a urine examination. At stated periods blood chemical examinations were done. The patients were followed indefinitely and the case was considered closed only if the patient could not be found after a careful investigation by our Social Service Department.

A mercury manometer was used. The cuff was placed in the upper portion of the child's right arm while recumbent. The arm bands were adjusted according to the size of the arm. The reading, when the first persistent sound was heard with the stethoscope, was recorded as a systolic pressure and the reading when the sound disappeared was recorded as a diastolic blood pressure. If the child seemed excited, readings were taken and were rechecked when he was calm.

The blood pressure was considered to be slightly elevated when the systolic was from 15 to 20 mm. of mercury above the normal; moderately elevated when it was from 20 to 40 mm. above the normal; highly elevated when it was from 40 to 60 mm. above and extremely elevated over 60 mm. The diastolic pressure usually followed the systolic figure, the range being from 10 to 15 mm. of mercury.

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From our experience, we believe the normal blood pressure values to be:

AGE	SYSTOLIC	DIASTOLIC
2-5 years	80-95	55
6-8 years	90-100	60-70
8-10 years	95-110	60-70
11-13 years	95-115	65-75
14-17 years	100-120	65-80

The severity of the illness during the hospital stay was estimated on the general clinical course which included the degree of edema, the height of the blood pressure, the blood urea nitrogen, and urinary findings. The children were then classified as having been mildly, moderately severe or severely ill. Twelve children were considered to have had a mild course, 33 a moderately severe course and 8 had a severe course.

Nine children were followed for less than 1 year. Twenty-two were seen at regular intervals for more than 1 year but less than 6 years, 11 were followed from 6 years to 10 years and 11 were seen from 10 years to 14 years (graph 1).

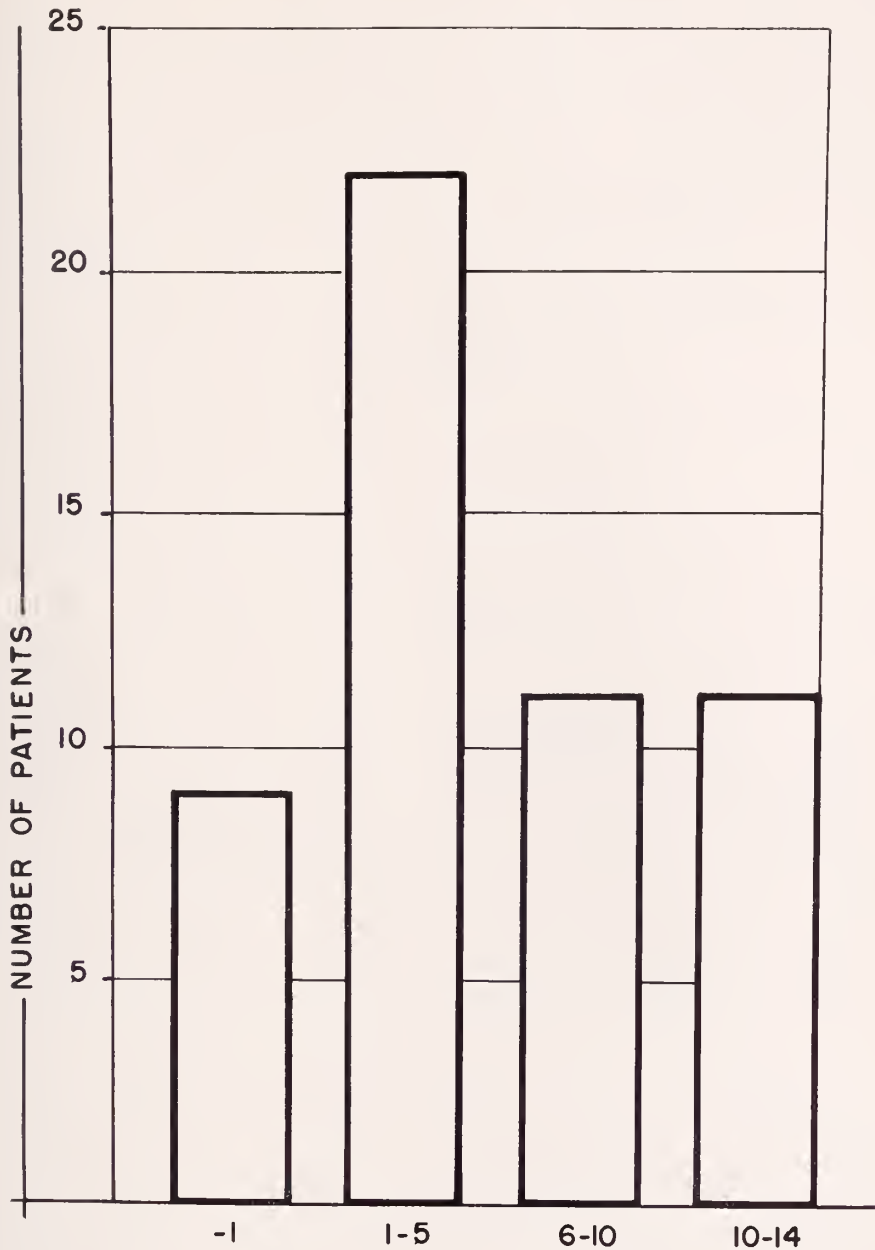
#### OBSERVATIONS

I. *Duration of elevation of blood pressure after the onset of acute nephritis without consideration of any other factor.* a) In 5 patients there was no elevation of blood pressure at any time; b) Nineteen had an elevated blood pressure which returned to normal before the first year. Of this latter group, 11 of the 19 had a normal blood pressure within one month; c) In 16 patients, the elevated blood pressure persisted for over 1 year. In 9 of these the blood pressure returned to normal in from 1 to 6 years and in 7 from 6 to 12 years; d) Thirteen had an elevated blood pressure when last seen, of whom 2 were seen less than 1 year, 5 from 1 to 6 years, 5 from 6 to 12 years and one fourteen years after the acute illness (graph 2).

*Impression.* The duration of elevated pressure after the acute nephritis was unpredictable when the height of the pressure alone was considered. However, in the majority the blood pressure returned to normal during the period of observation. The blood pressure reading did not, within three months after the original discharge from the hospital, exceed the figures considered to be moderately elevated, in any of the patients.

II. *Relationship of height of blood pressure on admission and its persistence.* a) There were 12 patients with normal blood pressure on admission. Of these, 5 never had any elevation, 2 had returned to normal; 1 within a month and the other at 1 year. Two were normal between 1 and 6 years and 2 were still elevated 8 and 11 years when last seen; b) Of 9 patients with slight elevation of blood pressure on admission, 2 returned to normal within 2 months, 2 within 5 years, and 1 within 12 years. When last seen, 4 had a higher blood pressure than when first seen (2 weeks, 1 year, 3 years, and 4 years); c) There were 8 children who had moderately elevated blood pressure on admission. Of these 5 returned to normal within 4 months and 3 returned to normal within 6 years, 8 years, and

10 years respectively; d) There were 14 children who had a highly elevated blood pressure on admission. Of these, 4 returned to normal within 5 months, 2 within

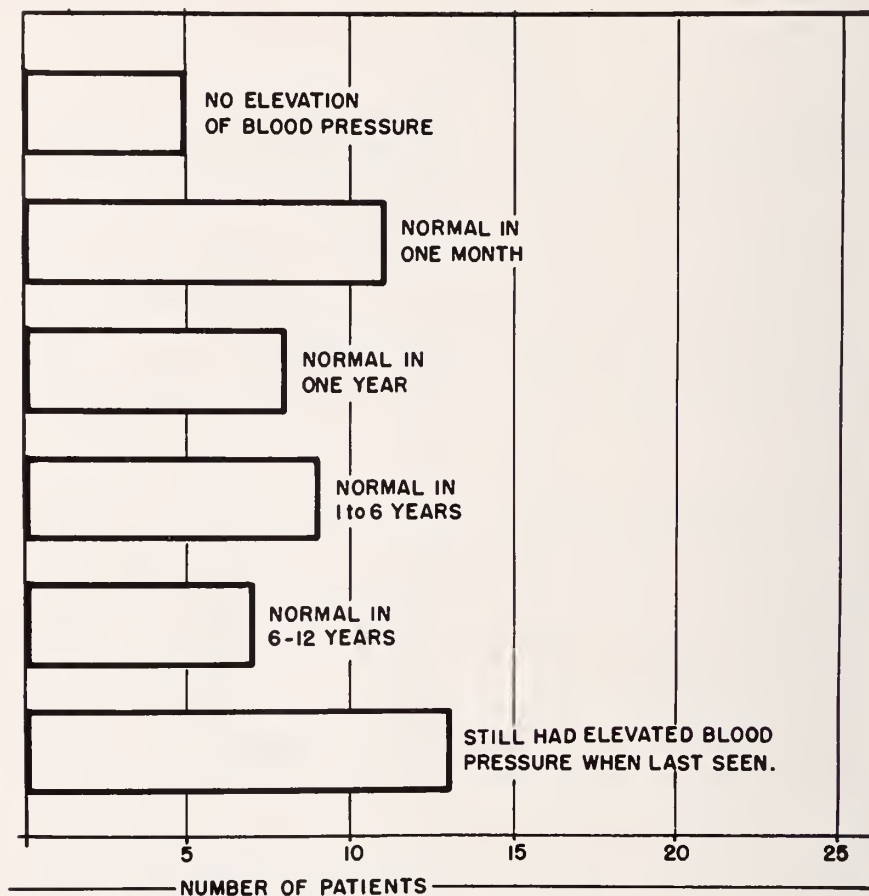


GRAPH 1. Shows duration of follow up in years after acute glomerular nephritis

4 years, and 3 within 8 years. There were 5 patients who still had an elevated blood pressure when last seen (5 months, 1 year,  $2\frac{1}{2}$  years, 10 years and 10 years); e) There were 10 patients with an extreme hypertension. Of these, 5

returned to normal within 1 year, 2 before 5 years, 1 before 8 years and 2 were still elevated when last seen (7 years and 14 years).

*Impression.* From these findings there seemed to be no relationship between the height of the original blood pressure during the acute stage and the height and duration of the elevation on the subsequent follow-up.



GRAPH 2. Shows duration of elevation of blood pressure after acute glomerular nephritis

III. *Relationship of the severity of the acute illness to the duration of the hypertension.* There were five patients with no elevation of blood pressure, four of whom had a clinically mild nephritis and 1 a moderately severe nephritis. Of 19 cases with an elevated blood pressure for less than 1 year, 7 had mild nephritis, 10 had a moderately severe course and 2 were severe. Of 16 who had elevated blood pressure for more than 1 year, 1 had a mild nephritis, 13 were moderately severe, and 2 were severe.

Of the 13 patients who had an elevated blood pressure when last seen, 1 had a mild nephritis, 8 had been moderately severe, and 4 had been severely ill.

*Impression.* The child with a clinically mild acute nephritis had less tendency towards a prolonged hypertension. There were exceptions, however.

We shall give a brief history of a child who had a mild nephritis and who was followed for 10 years. The blood pressure remained elevated until the last observation. This long period of elevation is unusual following an initial mild course:

L. A., a 4 year old white girl was admitted on April 1, 1933 with a mild acute glomerulonephritis following an acute tonsillitis. On admission the blood pressure was elevated (the systolic was 124 mm. and the diastolic was 80 mm.). The urine contained 2 plus albumin with many red blood cells and casts. The blood urea nitrogen was 15 mg. per 100 cc.

On discharge, 4 weeks later, the blood pressure was still elevated (the systolic was 115 mm. and the diastolic was 67 mm.). The urine contained a faint trace of albumin with occasional casts, white blood cells and red blood cells.

During a follow-up of 10 years the blood pressure remained elevated for a long period. At 6 years it was 120 mm. systolic and 60 mm. diastolic. At 8 years it was 120 mm. systolic and 90 mm. diastolic. At 12 years it was 142 mm. systolic and 105 mm. diastolic. At 14 years the blood pressure had returned to normal; the systolic was 120 mm. and the diastolic was 60 mm.

Except for an occasional finding of a trace of albumin and an occasional red blood cell, the urine examination was negative.

IV. *Relationship of persistence of albuminuria and elevated blood pressure.* We shall report on the urinary examination of 47 of the 53 patients. Six patients were excluded, since in our opinion the urinary examinations on follow-up were not satisfactory.

Twenty patients at the time of discharge had no albuminuria and these latter showed no albuminuria during the follow-up. Five had an albuminuria of from 6 months to one year; 14 from 1 to 6 years and eight from 6 to 14 years. a) Blood pressure readings on the 20 who had no albuminuria on discharge showed that 4 never had any elevation of blood pressure, 8 were normal within 1 year, 4 returned to normal respectively within 1 year, 4 years, 6 years, and 8 years. Four had an elevated blood pressure when last seen, 2 after 10 years, 1 after 4 years, and 1 after 1 year. b) In 5 who had no albuminuria, within 1 year the blood pressure returned to normal; in 2 within 3 months and 8 months, 1 had an elevated blood pressure for 2 years and then returned to normal and 2 had an elevated blood pressure for 3 years, and  $2\frac{1}{2}$  years when last seen. c) In 14 patients who had albuminuria from 1 to 6 years the blood pressure in 1 was still elevated after 1 year when last seen, 1 showed no elevation, in 6 the blood pressure had returned to normal within 1 year, and 6 others had an elevated blood pressure for 5, 6, 8, 10, 12 years before returning to normal. d) There were 8 who had albuminuria from 7 to 14 years. The blood pressure in one of these returned to normal after one month, in one elevated blood pressure persisted for 5 years before it returned to normal, in 2 for 8 years before it returned to normal. In 4 there was still an elevated blood pressure when last seen 7 years, 8 years, 14 years and 15 years after onset.

*Impression.* No clear-cut results could be recorded but it seemed to us that



when albuminuria persisted for long periods, the patient was more likely to have a persistent elevation of blood pressure. However, elevated blood pressure might persist after the disappearance of albuminuria.

V. *Relationship of the blood pressure to the edema.* Only 15 children had evidence of edema at the time of admission. Generalized edema was infrequent. Edema was present in all age groups. The 15 children were clinically classified as 1 mild, 11 moderate and 3 severely ill. All of the children with edema had an elevation of blood pressure during the acute period of illness. Nine children had a normal blood pressure on discharge from the hospital. Two had an elevated blood pressure for 8 years; 1 for 4 years, 1 for  $2\frac{1}{2}$  years, 1 for  $\frac{1}{2}$  year. One when last seen had an elevated blood pressure after 3 years.

*Impression.* If edema is present, an increase of blood pressure can be expected. Elevation of blood pressure may persist for several years before it returns to normal.

VI. *Puberty in relationship to changes in blood pressure in children with a previous acute glomerulonephritis.* There were 17 children who were followed through puberty. The age of the onset of the acute nephritis was from 2 to 5 years in 8, from 5 to 8 in 2, from 8 to 9 years in 5 and from 9 to 11 years in 2. Two were followed for 14 years, 3 for 13 years, 1 for 11 years, 5 for 10 years, 1 for 9 years, 4 for 8 years, and 1 for 7 years.

At the time of puberty, 8 patients had a normal blood pressure. Three who had a mildly elevated blood pressure did not show any rise during puberty. Four who had an elevated blood pressure showed an additional rise during puberty and 2 who had normal blood pressure before puberty showed a rise during puberty.

*Impression.* With increasing age there is a greater variability of blood pressure which is especially evident during puberty. We do not believe this variability is any greater in children with a history of a previous acute glomerulonephritis.

VII. *The course of pregnancy in individuals who had an acute nephritis during childhood.* We are interested in noting whether an acute glomerulonephritis during childhood would have an elevated blood pressure during the course of a pregnancy. We cite the histories of two such cases. In the one the blood pressure was elevated before puberty and still more elevated during and after. However, the blood pressure was normal throughout and after pregnancy.

In the other, the blood pressure remained elevated during the follow-up (from 11 years to 20 years of age). It then returned to normal and remained normal during and after pregnancy.

#### CASE REPORTS

*Case 1.* S. M., a 6 year old white girl, was admitted to the hospital on January 24, 1930 with the diagnosis of acute glomerulonephritis of moderate severity. On admission the blood pressure was systolic 108 mm. and diastolic 60 mm. The urine was smoky and contained albumin, red blood cells and casts. When discharged on February 30, 1930 after an uneventful recovery her blood pressure was systolic 88 mm. and diastolic 60 mm. The urine examination was negative.

At the age of 8 the blood pressure was systolic 125 mm. and diastolic 75 mm.; at 12 years systolic 120 mm. and diastolic 80 mm. At puberty (from 14 to 16 years) the blood pressure

was systolic 132 mm. and diastolic 78 mm. to systolic 140 mm. and diastolic 90 mm. At 18 years of age, when pregnant, her blood pressure remained normal (systolic 110 mm. and diastolic 70 mm.). One year later (5 months after the birth of her child) the blood pressure was systolic 122 mm. and diastolic 80 mm.

During the entire follow-up, urine examinations and blood chemistries were always normal.

*Case 2.* B.A. was admitted at the age of 11 years (on February 11, 1935) for a moderately severe glomerulonephritis which followed two weeks after an upper respiratory infection.

On admission she showed a mild degree of pretibial edema. The blood urea nitrogen was 48 mg. per 100 cc. The cholesterol was 250 mg. per 100 cc. The blood serum protein was 7.4 per 100 cc. of which albumin was 4.3 per 100 cc. and globulin 3.1 per 100 cc. The urine was smoky with large amounts of albumin, many red blood cells and granular and hyalin casts. The blood pressure on admission was systolic 130 mm. and diastolic 78 mm.

On discharge (May 6, 1935) the blood urea nitrogen was 12 mg. per 100 cc. cholesterol 250 mg. per 100 cc. Blood serum protein was 7.1 per 100 cc. of which albumin was 4.7 per 100 cc. and globulin 2.4 per cent. The urine was normal. The blood pressure was systolic 120 mm. and diastolic 90 mm. During 10 year follow-up her blood pressure remained elevated. At 12 years the systolic was 134 mm. and diastolic 80 mm.; at 14 years the systolic was 140 mm. and the diastolic 86 mm.; at 17 years the systolic was 150 mm. and the diastolic 94 mm. At the age of 20, the blood pressure returned to normal and remained normal during an uneventful pregnancy. The urine always contained a faint trace of albumin and occasional red blood cells.

#### DISCUSSION

An initial attack of acute hemorrhagic glomerulonephritis is usually preceded by an acute infection. When the nephritis is present, there is no recrudescence of the infection. This suggests that an antigen-antibody reaction initiated the renal lesion. Addiss (1) stated that the 3 cardinal signs of an acute glomerulonephritis were: 1) the gross appearance of the urine, 2) the edema, and 3) the hypertension. Hence at the very beginning, there is evidence of a widespread involvement. Addiss (1) also stated that the hypertension was the most readily available clinical index of generalized extra renal abnormalities of the initial stage. In acute glomerulonephritis, the assumption is that there is a generalized spasm of the arterioles. Lichtwitz (2) believed there was also a closure of the small veins and a paralysis of the capillaries; hence an increase in blood pressure. Cardiac dilatation is not an infrequent finding. The mechanism of this generalized ischemia is not clear but it is believed, by some, to be due to the action of a pressor substance (renin) produced from the diseased kidneys.

It has been established that there is complete clinical recovery in most children with acute glomerulonephritis. Undoubtedly a small number of the nephrons are permanently damaged, the remainder heal entirely so that there is sufficient kidney tissue to carry on. If careful microscopic examinations of the urine are made, one often finds increased formed elements for as long as 6 months after the acute attack. In some the sediment is normal in from 4 to 6 weeks. Only in 2 per cent to 8 per cent does the nephritis develop into a subacute or chronic stage.

In this communication we have attempted to ascertain the significance of the blood pressure reading in children during the acute nephritis and on subsequent

follow-up examinations. From our observations, there appeared to be no relationship between the height of the blood pressure during the acute illness and the duration of the increased blood pressure. Occasionally, a child who had a normal blood pressure during the acute illness would have a subsequent rise for many years. In this series there were two such children.

There seemed to be some relationship between the severity of the acute illness and the duration of the hypertension. Did this latter finding imply that the damage in severe illness on the smaller blood vessels was more extensive and therefore it took a longer period for these vessels to return to normal?

Does the prolonged presence of albuminuria have any relationship to continued elevated blood pressure? There is no constant relationship, but one gets the impression that with albuminuria, there was more probability of prolonged elevated blood pressure. It should be noted that in a number of patients the elevated blood pressure persisted after the urine became albumin free.

It also seemed apparent the elevated blood pressure was more likely to persist when moderate edema was found during the acute stage.

Longcope, Bordley and Lukas (3) described a group of patients with essential hypertension following an acute glomerulonephritis. Kidney function tests were normal. We found no such patients. It is of interest to note that we did not find any child with a high degree of hypertension after the first few months following the acute illness.

According to our observation following an acute nephritis—a moderate elevated blood pressure may persist for varying periods without any objective symptoms or abnormal urinary findings. Therefore, a moderate increase of blood pressure should not be taken as an index of kidney damage.

#### SUMMARY AND CONCLUSIONS

1) Fifty-three children were observed during an acute glomerulonephritis and their blood pressure reading followed for varying periods of time after their discharge from the hospital.

2) In 40 patients the blood pressure returned to normal levels during the period of observation.

3) The duration of the elevation of blood pressure was unpredictable.

4) The tendency to prolonged elevation of blood pressure was seen more frequently after a severe glomerulonephritis.

5) When the albuminuria persisted for long periods, the patient was more likely to have a persistent elevation of blood pressure. Prolonged albuminuria with or without moderate elevation of blood pressure should not necessarily be a cause for alarm. In some children the hypertension persisted after the disappearance of albuminuria.

6) When moderate edema was present during the acute phase, increased blood pressure frequently persisted over varying periods.

7) In 11 of 17 patients there was no rise in blood pressure during puberty.

8) A moderate elevation of blood pressure for long periods gave no clinical symptoms.

9) A moderate increase of blood pressure alone even over long periods should not be taken as an index of kidney damage.

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# OBSERVATIONS ON THE USE OF DIGITALIS IN THE TREATMENT OF CHRONIC CONSTIPATION AND ALLIED CONDITIONS

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It is a great privilege to participate in the dedication of a memorial volume in honor of the late Dr. Albert A. Berg. No accolade bestowed on any man can be finer and more significant than the genuine appreciation of his colleagues for his great service in the art to which he has devoted his life. It is given to but few to enjoy during life the fruits of their labors deservedly, and in such measure as has been given to Dr. Berg.

The subject which I have chosen to write about is not romantic. It is only remotely related to the special field of surgery in which Dr. Berg has attained pre-eminent success; but, it constitutes an every day problem in medical practice, and must be dealt with.

As the title indicates, the subject concerns observations on the use of digitalis in the treatment of chronic constipation, distention, and other forms of intestinal stasis; conditions which sometimes lead to surgical intervention, or arise therefrom.

Today, when so much is presumably known concerning the action and the use of digitalis, the suggestion that it can be employed for the control of intestinal stasis may appear anachronistic. However, my experience with digitalis in the treatment of such conditions, and the successful results attained in many intractable cases of chronic constipation, justifies my belief in the propriety of the suggestion. The idea embodied in it is in no way iconoclastic. Digitalis, as is well known, has a number of side reactions. The present discussion deals with one of them; namely, the effect of digitalis on the motility of the small and large intestine. It will be shown that this effect, reduced to physiologic dimensions, has a definite place in the treatment of the conditions mentioned above.

Ever since Withering (1778) introduced digitalis into clinical medicine, its use has been entirely restricted to cardiologic problems. Its effect upon other organs, notably the gastro-intestinal tract has come to be regarded as evidence of toxicity or over-dosage. It is to this aspect of the action of digitalis and its therapeutic potentialities that I wish to direct attention in this paper.

Many years ago when I was an intern at the hospital I gained the impression that patients receiving digitalis for cardiac and circulatory conditions were less prone to suffer from intestinal stasis, and required the nightly cathartic (cathartic rounds were then the order of the day) less often than other patients in a like or comparable state of debility. In the light of modern cardiologic standards, the dosage, as I recall it was at no time excessive.

Subsequent experience in private practice confirmed this impression. Finally, a chance remark on the part of a patient led me to explore the question further. The patient, a veterinary surgeon, was given digitalis in accord with the tenets of the day, for cardiac failure associated with hypertension. Some weeks later this patient asked me whether I had prescribed digitalis for his "heart" or for

his "stomach." When I inquired as to the reason which prompted his question, he stated that he had been passing a great deal of flatus. At the same time he informed me that it was a common practice amongst veterinarians to administer large doses of digitalis, as much as an ounce of the tincture per rectum to horses, in order to combat "wind-colic", a common and often fatal malady amongst these animals. The dose which I had prescribed for this patient was certainly not excessive, and, in the absence of other symptoms (nausea, vomiting or diarrhea) the action on the bowel which he had mentioned could not be regarded as toxic in origin. This supposition led me to believe that under certain conditions, digitalis might have a specific effect upon the bowel which in some respects, was comparable to that upon the heart.

A search of the literature for information on the subject proved rather disappointing. My original observations were made in 1910, and I found in the literature only one paper by E. Magnus (1) dated 1905 which was relevant. This author drew attention to the stimulating effect of digitalis derivatives on the muscular coat of the intestine. He indicated furthermore that this effect was independent of its nerve supply, and could not be retarded by atropine or other nerve paralyzing agents. Later investigators confirmed these conclusions.

These facts taken together with my own observations and the information which the aforementioned patient imparted to me, seemed to contain the germ of an idea which might be applied usefully in clinical medicine.

There are a number of therapeutic agents which are employed for specific purposes that are endowed with side reactions: some good, some bad. The margin between the desirable and the undesirable effect is often narrow. The action of digitalis on the gastro-intestinal tract has always been considered toxic and undesirable. As a result no systematic effort has been made to explore adequately the therapeutic potentialities of the side reactions of this drug in respect to these organs. Apart from its effect upon the heart, pharmacologists and clinicians were unanimous in their opinion that when digitalis is administered by mouth, rectum or parenterally, in excess of the therapeutic requirements, or the special tolerance of the individual, it creates certain disturbances in the alimentary system.

Hatcher and Weiss (2, 3) have demonstrated that the emetic action of digitalis derivatives is not exerted on the stomach or the intestines directly. According to these authors the nausea and vomiting resulting from digitalis intoxication, are due to the direct action of the drug on the heart and not to an irritant effect on the gastric mucous membrane. The afferent impulses from the poisoned heart are conveyed to the vomiting center in the medulla largely through the sympathetic nerves, in part perhaps, by way of the vagus. No similar evidence of any effect on the intestines has been adduced.

In the middle 20's, a number of publications appeared dealing with the rectal administration of digitalis in the treatment of special cases of heart disease (4, 4A, 4B). It has been shown that in certain cases, large doses of the drug up to 20 cc. of the tincture, can be used daily without producing any ill effects (5, 6).

In another series of contemporary publications experimental studies on the effect of digitalis upon the intestinal musculature were carried out (7). The most

noteworthy of these were the studies of Korda (8). This investigator observed that digitalin and digitalis-like substances had a direct effect on intestinal peristalsis. He found amongst other things that instillations of digitalin into the lumen of a loop of small intestine of the horse, or into sections of the large intestines of smaller animals provoked definite intestinal movements. These movements consisted of two phases; namely, a longitudinal and a transverse or circular movement. The longitudinal motion is of a pendular character by means of which the intestine is alternately shortened and lengthened. The transverse contraction proceeds rhythmically along the length of intestinal loop. In other words, the resulting motion resembled normal peristaltic movements. In Korda's opinion the peristalsis brought about by digitalin, as previously suggested by Magnus, is by its direct action upon the muscularis of the intestine, and, not through the intervention of its nerve supply. Thus, on experimental grounds there is agreement that digitalis can excite or activate peristaltic movements in the intestinal muscles.

Whether (9) or not (10) the nerve supply actually participates in the normal peristalsis of the intact bowel is an academic question. Our interest lies chiefly in the reality of the response which the administration of digitalis can produce.

According to Korda it is very significant that the degree of response which the instilled digitalin provokes in different parts of the intestine, depends upon the site where the stimulus is applied. It becomes more intense the further away it is from the stomach. In addition this investigator found that large doses of the drug produce a paralytic standstill of the intestinal loop, and abolish completely its peristaltic movement. This is comparable to the effect which excessive doses of digitalis can produce upon the heart.

However, none of the authors suggest the possible use of digitalis in the treatment of intestinal conditions. But the knowledge of its special use in veterinary medicine prompted me to investigate whether or not a similar application could be made in clinical practice. A preliminary trial in a few selected cases with the rectal administration of digitalis indicated that actually such use of it could be made for the specific purpose of inducing or activating normal peristaltic movements of the bowel, without causing any demonstrable ill effects in any other part of the body. Further observations revealed that this procedure was surprisingly effective in correcting various static conditions of the bowel, including chronic constipation. Many of the latter type of case so treated had previously proven refractory to all other methods in general use. It was found moreover that this remedy provided more than temporary relief to the patients, and was actually curative in a number of them.

As in veterinary practice, the preliminary trials on patients were made with the tincture of digitalis. Four cc. of the tincture, diluted with 60 cc. of water were instilled into the bowel. While this dosage was purely arbitrary, the results were none the less highly satisfactory. Consequently it was retained as a standard in subsequent applications. But, as the primary object of the undertaking was to ascertain the effectiveness of the digitalis proper, the tincture was discarded in favor of the fluid extract. This was done in order to obviate any question of the

supplemental action of the alcohol contained in the tincture. The amount of extract used was approximately equivalent to the drug content of the tincture.

Like the tincture, the fluid extract of digitalis is a crude preparation and contains a number of substances which influence each other's solubility and pharmacologic action. The reputed action of digitalis, however, cannot be ascribed to the multiplicity of substances present in it, because similar effects can be produced by the individual derivatives of this substance. Corroboration of this can be found in the experiments of Korda on the effect of digitalin which were cited above.

The rate of absorption of digitalis from the rectum (11, 12) is believed by some to be of the same order as that which follows oral administration. Others are of the opinion that it reaches the body at a faster rate when administered by rectum. The difference is ascribed to the fact that the rectum is provided with a dual circulation.

The blood supply of the gastro-intestinal tract above the rectum is such that all venous blood flows into the portal vein, thence, via the liver, reaches the general circulation. The rectum on the other hand is supplied by the hemorrhoidal plexus, as a result of which the blood follows into two channels. One of these, comprised of the middle branches, empties into the vena hypogastrica (internal iliac) and then directly into the general circulation. The rest empties into the portal circulation. It is reasonable to suppose, therefore, that excretion of the drug by the kidneys may also proceed faster when administered by rectum, than it is when given by mouth.

In order to procure the desired effects in the treatment of intestinal disorders, the same rules which govern the clinical use of this remedy in heart disease must be observed. The normal heart is believed to be refractile to digitalis. The dosage of the drug needed for therapeutic purpose in diseased hearts is as stated before, rather large—a condition which may affect the intestinal tract adversely. On the other hand the amount of digitalis needed in intestinal therapy is comparatively small, and incidental action on the heart is highly improbable.

Qualitatively, the margin between the therapeutic and toxic effects is precisely the same; but quantitatively they are different, because the therapeutic threshold of the intestine is lower. Full appreciation of this fact makes the utilization of digitalis in intestinal conditions feasible.

In the treatment of heart disease, a certain optimum concentration of digitalis in the body must be reached and maintained to procure the desired result. In intestinal therapy that is not so. It is the specific effect of the individual dose that counts. For it has been found repeatedly that normal movements of the bowel follow one or two treatments with digitalis which are spaced days apart. This would seem to indicate that the effect of this remedy is in the nature of a "trigger" action, which sets off the normal propulsive movement of the intestine. The prolonged or continuous effect so necessary in cardiology is not required in intestinal therapy. However two rules are essential for success—namely an adequate dose of digitalis and proper spacing of the treatments. But the amount of digitalis actually required for intestinal therapy is far below that needed for



cardiac purposes; and allowing for the quantity which the kidneys can dispose of, the concentration of digitalis in the body after each treatment is probably very small. Under these circumstances, (unless an unusual idiosyncrasy exists) cumulative action is unlikely, and the chance of digitalis poisoning is virtually nil. The best proof of this is the fact that not a single instance of that was encountered in all the cases treated over the many years.

The cases that were treated represent various forms of intestinal stasis. Exclusive of mechanical factors, (post-operative adhesions, abdominal tumors, etc.), which can interfere with the passage of intestinal contents, the causes which produce them are also numerous. It would take me too far afield to discuss them all in detail. The causes most commonly encountered are: asthenic habitus, redundancy of the colon, hypothyroidism, sedentary habits, dietary inadequacies, visceroptosis, colitis which is either idiopathic or that induced by the habitual use of cathartics, enemata and colonic irrigations. While the results that can be attained by treatment in the different types of stasis may vary, nevertheless it is safe to assert that digitalis may be employed in all of them, without regard to their etiology.

It is the colon of course, which presents the major problem in intestinal stasis. Upon examination it is usually found to present different degrees of distention, or spasm, or both. On the whole, the results which digitalis therapy yields are usually better and more readily achieved in the atonic than in the spastic type of stasis. Not infrequently the first or second treatment gives an indication of the efficacy of the procedure and its ultimate success. The spastic type is more refractory. Finally however, the normal peristaltic rhythm can be re-established, and the stimulus or excitation which the intestinal contents ordinarily provide becomes normalized. The movements then proceed in an orderly fashion.

An analysis of the cases indicates that six to twelve treatments are necessary to produce the desired motility of the bowels. In some patients two or three are sufficient. As already mentioned, it is usually the spastic type that requires the longer course, and, in a few particularly refractory cases the duration of the treatments may have to be extended considerably.

Some patients make a fetish of catharsis and the daily bowel evacuation becomes an obsession. In many instances this is the result of medical direction by physicians, or popular misinformation; but very often the aforesaid individuals are the victims of commercial exploitation.

In the course of the treatment all cathartics are interdicted, and antispasmodics are not used. Ordinarily a bowel movement or even two occur within 24 hours after the first treatment. But in the cases just referred to, namely the spastic type, the use of a glycerine suppository after the first, second, and rarely the third treatment is permitted, in order to initiate the evacuation. In this way the patient's fears are allayed, and, confidence in the outcome of the therapy is established. Another very important feature which speaks for the correctness and efficacy of the treatment is the fact that dietary regulation, supplemental aids, or change in the patient's habits are not required in order to achieve a successful result.

The steps in the treatment are as follows:

1. One half cc. of the U.S.P. fluid extract of digitalis is diluted in two ounces of warm water.

The amount of digitalis suggested here has been found to be sufficient in most instances, but it is well to remember that the potency of digitalis preparations is often variable. It is therefore necessary to have prior knowledge of the source, quality and strength of the preparation that is to be used.

2. With the patient lying on the left side and the knees drawn up, a #12 French soft catheter, properly lubricated, (preferably dipped in oil) is inserted into the rectum for a distance of about 8 inches.

3. By means of a small bulb syringe the fluid is slowly instilled into the bowel and then the catheter is carefully withdrawn. The patient is rarely aware that any medication has been administered.

4. The object of the small volume of fluid used and the slow rate of instillation is to avoid sudden distention of the bowel, and the risk of having the medication expelled. One other point sought by the procedure is to obviate as far as possible the irritation of the anal sphincters, (which can cause tenesmus), and make the retention of the medication difficult. These precautions are necessary in order to insure the therapeutic effect of the medication.

5. The treatments are usually spaced at 2 to 4 day intervals; occasionally the intervals are lengthened. The patient receives 3 treatments during the first week; during the second week, 2 treatments, and thereafter, one or two treatments until regular daily movements occur spontaneously. It is important in this connection to inform the patient, particularly one who has been taking, or receiving enemata, that the treatment is not an ordinary enema, and further, that it is not intended to cause an immediate evacuation of the bowel. In the vast majority of cases, the instilled medication causes no desire for an immediate movement. In any event, it is well to instruct a patient to try to retain the instillation for an hour at least, and that a movement may be expected within 24 hours.

It must be made plain too, that the object of this therapy is the restoration of a normal peristalsis of the bowel, and nothing else. Properly applied the treatment causes no discomfort to the patient. The stools are usually of normal consistency, and the movement is not accompanied by any strain, pain or colic. Diarrhea has at no time been encountered.

The problem in the treatment of abdominal distention in the course of infectious diseases (pneumonia, etc.) or following an operation is naturally different from that presented in the treatment of chronic constipation. Ordinarily the condition is acute and prompt relief is desired. When other methods are unavailing, digitalis is administered as described above, and an hour or two later, a catheter or rectal tube is inserted into the rectum for the relief of the distention.

The administration of digitalis can be used prophylactically also where medication of a binding character, such as opiates, iron, etc. is indicated, and the development of constipation is anticipated.

Occasionally certain of the treated cases return many months or even several years later, complaining of some retardation of bowel motility, induced very

often by change of environment, occupation, or other contributory factors. The difficulty is overcome after a very short "refresher" course consisting of two or three treatments. Certain others, because of fear that the original constipation might return, come back regularly once or twice a year to receive a treatment.

In view of the fact that the treatment described in this paper was conceived and even instituted many years back and continued up to the present, it is reasonable to assume that the clinical material accumulated in the intervening years is quite extensive. A statistical review of all the cases treated would hardly serve any useful purpose. Instead, I shall confine myself to a description of a few of them.

The cases to be presented were selected deliberately and will be summarized briefly. In most, the malady was of long standing and in some was associated with other complaints. In all, the complaints were of long duration, and all had received the benefits of accepted methods of treatment without enduring results.

Most important is the fact that the cases to be cited have been under prolonged observation. The merit of the treatment could thus be ascertained—a condition necessary in the evaluation of any therapeutic procedure.

#### CASE REPORTS

*Case #1.* R. Y., a female, aged 39, consulted me originally in 1924, and along with case #5 is typical of those who return for "refresher courses". The patient's main difficulties at the time of her first visit were listlessness, headaches and constipation. After ruling out the possibility of any organic disease, a series of twelve to fourteen treatments were administered with very satisfying results. This patient has returned regularly, up to the present, every two or three years for a few treatments, varying in number from six to eight at a time; given at three to five day intervals.

*Case #2.* P. F. In 1928 a woman, 65 years of age, came under my care. She was suffering from hypertensive cardiovascular disease and recurrent severe anginal attacks. In addition she suffered from marked constipation, due to anorexia and consequent loss of weight; a visceroptosis had resulted. The anginal attacks became so severe that even the frequent administration of nitrites offered no relief. The physicians in charge withheld the use of opiates because of the obstipation and fear of intestinal obstruction. Digitalis therapy by rectum was instituted and the obstipation was relieved, so that adequate medication for the angina was made possible.

*Case #3.* E. J. S. In 1928 a woman aged 54 years came to see me giving a history of life-long constipation which had increased progressively. She had been taking cathartics for many years. Physical examination revealed nothing of an organic nature. This patient received thirteen treatments and had no further difficulty until 1930 when she returned for two treatments.

*Case #4.* R. J., a man, 36 years of age was referred to me in 1930. Previous medical history was negative. The present complaint was that of constipation of five years duration associated more recently with pyrosis and eructations. X-ray examination revealed no organic pathology. Physically there were no definite findings except a markedly spastic sigmoid. The patient was given seven treatments at three to four day intervals with excellent results.

*Case #5.* E. D., a woman consulted me at the age of 36 in 1929, giving a history of constipation extending over many years which had become aggravated since the birth of her last child six and a half years previously. She admitted taking a variety of cathartics and frequent enemas. The only positive findings on examination were a visceroptosis and a retroposed uterus. The basal metabolism was low. She was given small doses of thyroid which she has taken on and off until recently.

This patient received ten treatments with good results. When she returned towards the latter part of 1931, she stated that she had been "absolutely cured" until very recently when she had taken a trip and had experienced a recurrence of her constipation. On this occasion three treatments sufficed and she did not return with her original complaint until 1933 when four treatments were required to clear up the condition.

This woman is one of those who is extremely "bowel conscious" and as a result she comes in regularly once a year or so for a few treatments. The number has varied from three to six at a given time. She was seen as recently as December 1949.

It is of interest in this particular case that, as stated in the physical examination at the time of her first visit, a retroposed uterus was noted and was suspected of playing a part in the constipation. Subsequently, a fibroid developed for which a hysterectomy was done, four years ago. The removal of the uterus appeared not to have influenced the tendency to constipation.

*Case #6.* K. R., a man, 49 years of age consulted me in 1941. Several years prior he had had two episodes of bleeding from a duodenal ulcer, with no subsequent recurrence and no further symptoms. The complaint at the time I saw him was that of constipation. Physical examination was essentially negative. This patient received six treatments and had no further complaints referable to his bowels until 1946. At this time he had gained considerable weight, and a basal metabolism was done. It was found to be Minus 20%. While a small dose of thyroid was prescribed, the patient did not take it. In addition, he received three treatments and has remained well since then.

*Case #7.* R. V., a woman 45 years of age, who was referred to me in 1941 stated that she had a feeling of fullness in the abdomen, and was markedly constipated. The previous medical history was negative except for an allergy to certain protein foods. An appendectomy and a hysterectomy had been performed several years prior to her visit. A "resection of the bowel" had been done in 1940 for a redundant colon associated with "so-called intestinal toxemia". This patient had received colonic irrigations at regular intervals since then.

Physical examination revealed a thin pale woman. There was no adenopathy. A friction rub was heard along the right border of the heart; fluoroscopically the heart was shifted to the right and the left diaphragm was elevated. Abdominal examination revealed the scars of the previous operations, felt doughy, and was tympanitic. No masses were felt. A previous chest plate as well as the gastro-intestinal films were reviewed. The former revealed numerous calcified small nodules and decided elevation of the left diaphragm. The gastro-intestinal series showed an extreme redundancy of the colon and marked ballooning out of the ileo-caecal valve. An electrocardiogram done in 1941 showed myocardial changes without any symptomatic complaints.

This patient was given three treatments with success; then the period between treatments was lengthened to from 4-5 days. After the sixth treatment she was instructed to return in two weeks. She had gained weight, felt well and within the ensuing two months, she received six treatments all told. Several months later she had a recurrence of her constipation associated with some gastric symptoms. Bland powders and three or four treatments promptly alleviated her difficulties. Although seen at regular intervals since then and as late as February 1950 for minor complaints, she has had no recurrence of her bowel disturbance.

*Case #8.* M. K., a man of 43 years of age consulted me in 1942, giving as his chief complaints nervousness and constipation. The past history was irrelevant except for the fact that he had been a heavy smoker and drinker, but had stopped both several weeks before coming to see me. The salient points of the physical examination were that of an obese, plethoric individual with a hypertension, an enlarged and rapid heart, and a diffusely dilated aorta. Abdominal examination except for some distention, was negative.

In addition to the regime instituted for the hypertension, this patient received nine treatments for his constipation with the result that his bowels moved regularly. He was seen on several occasions in 1943, at which time he had resumed drinking and smoking, but had no bowel difficulties. Several electrocardiograms taken since 1945 showed left



ventricular preponderance, a sinus tachycardia and an occasional premature ventricular contraction. In March of 1944 he experienced a recurrence of his constipation and received two more treatments. To date he has had no more difficulty. Since 1944, this patient has come in for regular check-ups. Very recently his complaints were distress in the epigastric region associated with eructations. X-ray of the gall-bladder was negative, while that of the gastro-intestinal tract showed a healed duodenal ulcer. It is interesting to note that for a day or two following the administration of barium in the course of the gastro-intestinal examination, there was slight irregularity of the bowels, which since then has cleared up, and no further treatments were necessary.

*Case #9.* L. K., originally seen in 1921, a woman 31 years of age, has been under my care for the past 29 years. While she has never had any serious illnesses, she is the type of patient who always has a multiplicity of complaints. One of the outstanding ones was that of constipation dating back to childhood. She had been, and continued throughout these many years taking cathartics and having colonic irrigations in the belief that nothing else could relieve her constipation. It is interesting to note that this patient had a low basal metabolism which was checked at regular intervals, and that the simple administration of thyroid had no effect upon the bowel condition.

In spite of many discussions with her as to the desirability of discontinuing the above methods in favor of a course of treatments with digitalis, it was not until November 1949 that she was willing to accept my suggestion. She was somewhat rebellious when informed that all cathartics and colonics must be discontinued. When, however, after five or six treatments she began to see results, the patient seemed convinced of their efficacy. A few more treatments were administered and since then the bowels have been moving regularly.

*Case #10.* R. W., a woman, aged 65, consulted me for the first time in April 1950 and gave a history of epigastric distress, eructations, pain in the right iliac region and flatulence. The bowels had been constipated for many years and cathartics had been resorted to. Ovarietomy and appendectomy had been performed in 1929. She had been under the care of a gastroenterologist, and roentgenologic studies revealed no special pathology. Physically the only positive findings were distention of the abdomen and generalized tenderness, particularly over the cecum. A marked anemia was found and hematinics were prescribed.

This patient received only two treatments. After the first, she volunteered the information that her abdominal pain had subsided and that her bowels were moving regularly, and to date there have been no further complaints referable to the bowel.

#### SUMMARY

The preceding clinical study was based on the hypothesis that the alleged toxic action of digitalis on the alimentary tract represented merely an exaggeration of its pharmacologic potentialities, which could be harnessed to serve a useful therapeutic purpose.

The exact mechanism by which digitalis reestablishes normal peristalsis is still problematic. It is conceivable that in the atonic intestine it may stimulate the function and strength of the stretched and enfeebled muscle fibres, in very much the same manner as it does in the dilated heart. But in the spastic type its role may be different. It is possible that in this condition, digitalis serves to break a "vicious cycle", which prolonged irritability of muscular or neural origin may have established.

The suggested use of digitalis in intestinal conditions offers a method of treatment of exceptional merit which has heretofore been overlooked.

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# THE RICE DIET IN THE TREATMENT OF THE AMBULATORY HYPERTENSIVE PATIENT\*

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The increased interest in dietotherapy of hypertension (5-9) resulted in the referral of many patients with hypertensive vascular disease to the Nutrition Clinic of the Mount Sinai Hospital. This report presents the results obtained in a group of 35 patients treated with the Kempner rice diet (8), during the past 3 years. The duration of treatment was 2 to 24 months, average 10.3 months. The group was selected by the following criteria: 1) duration of hypertension of at least 1 year; 2) observation in the Hospital (out-patient-department) for hypertension during a control period of at least 6 months; 3) minimum systolic pressure of at least 170 mm. Hg. and diastolic 100 mm. Hg.

All patients were ambulatory and presented problems of management different from those of the hospitalized patients, or private ambulatory patients. They belonged to a very low income group, and special diets meant a difficult financial problem, requiring additional "diet allowance". In many instances, language difficulties had to be overcome because of the varied racial and national character of the group (Jewish, Puerto Rican, Negro, Italian and German). Of the 35 patients, 30 were females and 5 males. The age ranged from 37 to 72 years (average 57.3). With the exception of one patient who had chronic glomerulonephritis, all had hypertensive vascular disease in the benign phase.

Information concerning the known duration of hypertension was obtainable in 34 patients. It ranged from 1 to 16 years (average 7.3). The length of observation in the out-patient-department, prior to instituting the special diet was 6 months to 4 years (average 2 years). The systolic blood pressure during the control period ranged from 170 to 245 mm. Hg. (average 208) and the diastolic from 102 to 143 mm. Hg. (average 118).

During this control period, the patients were treated in the customary way: they were advised to rest as much as possible, to avoid hard manual work, to adhere to a low salt diet of approximately 2 grams daily, and to use small doses of sedatives such as phenobarbital, often in association with theobromine or aminophyllin. During this time, the blood pressure was taken and recorded at regular intervals. Patients who evidenced marked fluctuations in blood pressure levels during the control period, were not included in this study. This group then consisted of hypertensive individuals whose blood pressure became well stabilized before the rice diet was begun.

Thus in this study each patient served as his or her own control during a period of at least 6 months under ambulatory conditions. Individual controls over a prolonged period of time are in our opinion preferable to group controls consisting of different persons with different individual variations. The majority of the

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patients of this group were overweight. The degree of obesity varied considerably. The lowest actual weight before the rice diet was started was 116 lbs., and the highest 246. The average actual weight was 174 lbs. The average ideal weight was 132.8. Thus the average weight of the group was 31% higher than the average ideal weight.

#### METHODS

The diagnostic study included: physical examination, study of the fundi, electrocardiogram, basal metabolism, urine analysis, Fishberg concentration test, blood count, Wassermann test, and the following chemical analyses of the blood: sugar, urea nitrogen, serum chloride, serum cholesterol, and serum total proteins.

After completion of the diagnostic studies the patient was interviewed by the physician and was given careful instructions as to the advantages and difficulties of the dietary regimen. Special emphasis was placed upon strict observance and close cooperation with physician and dietitian. It was further stressed that a certain monotony of the diet was unavoidable, and adherence to this regime required unusual energy and will power over a long period of time. If, despite this warning, the patient consented, a more detailed explanation of the diet was given by the dietitian in both oral and written form.

The special diet consisted, as originally recommended by Kempner (8), of rice, fruit, fruit juices and sugar supplemented by vitamins and iron. The daily caloric content was approximately 2000 calories with carbohydrate 450 Gm., protein 20 Gm.; fat 5 Gm.; sodium 0.2 Gm.; and chloride 0.15 Gm. The fluid intake was limited to 800-1000 cc. of fruit juices.

To introduce a certain variety to the diet, a menu with alternate choices of fruit and rice dishes was given to the patient. On each subsequent visit to the clinic, the diet was carefully discussed, and modifications were made when indicated. A typical menu consisted of 3 main meals, breakfast, lunch, dinner, and supplementary feedings around 10 a.m., 4 p.m. and before retiring. Diet form and model of menu are presented in Table 1.

The patients returned to the clinic at regular intervals, in the first 6 weeks weekly, and later at intervals from 2-3 weeks. On these occasions, they were interviewed and examined by the same physician. Changes in symptoms and weight were carefully noted; several blood pressure determinations were made in the sitting position of the patient with the purpose of obtaining a "basal relaxed level" in the sense of Ayman (2); blood was drawn for repeated chemical analyses.

On each visit, the patient brought a "before breakfast" specimen of urine which was tested qualitatively for chloride concentration. We are fully aware of the fact that this test represents only a practical substitute for the more important urinary sodium concentration. However, it proved to be of great advantage in estimating the patient's cooperation. The application of this chloride test precluded, of course, the use of any salt substitutes which contain chloride.

The urinary chloride test was performed in the following manner: to approximately 5 cc. urine in a test tube, 5 cc. of the reagent was added.<sup>1</sup> The resultant

<sup>1</sup> A more quantitative approach as suggested by Bryant, *et al* (4) is being used at present.



precipitate of silver chloride was evaluated on a 1-4 plus basis, in a similar manner as the degree of proteinuria is usually estimated. The reagent consisted of:

Concentrated Nitric Acid.....	40.0 cc.
Silver Nitrate 12%.....	40.0 cc.
Distilled Water q.s.....	ad 500.0 cc.

After an interval of approximately 2-4 weeks and depending upon the previous salt intake, the urinary chloride excretion decreased to trace or 1 plus. Readings

TABLE 1  
*The Mount Sinai Hospital, New York. Nutrition Clinic. Rice Diet.*

NAME..... DATE..... 195

Follow your diet very closely and do not eat foods which are not included or specified.

AVOID: Salt, seasonings, milk, butter, fats, or fat drippings, shortenings, salad oils, coffee, tea, other beverages, nuts, dates, figs, avocados, tomato juice, vegetable juices, and all canned or dried fruits to which substances other than sugar have been added.

USE: White sugar, pure honey for flavoring.

BREAKFAST	
<i>Amount</i>	<i>Suggested items of Food</i>
1 Portion fruit, stewed or canned	4 Prunes
1 portion fruit, fresh	½ Grapefruit
¾ cup boiled white rice	
4 ounces orange juice	
4 ounces prune juice	
3 teaspoons white sugar	
1 multi-vitamin pill	

LUNCH	
1½ cups boiled white rice	
2 portions fruit, stewed or canned	Peaches, cherries
1 portion fruit, fresh	Apple
8 ounces fruit juice	Pineapple juice
3 teaspoons white sugar	
1 multi-vitamin pill	

DINNER	
1½ cups boiled white rice	
2 portions fruit, stewed or canned	Pineapple, berries
1 portion fruit, fresh	Pear
3 teaspoons white sugar	
8 ounces fruit juice	Apple juice
1 iron pill	

SUPPLEMENTARY FEEDINGS	
(mid-morning—mid-afternoon—bedtime)	
1-2 Portions fruit, fresh	
3 Ounces fruit juice	

Table 1.—*Continued*  
CHOICE OF FRUITS AND FRUIT JUICES  
*Average Portions*

<i>Fresh Fruits</i> (may be stewed)		<i>Canned Fruits</i>	
Apple, 3" diam . . . . .	1 large	Applesauce . . . . .	$\frac{1}{2}$ cup
Apricots . . . . .	2-3 medium	Apricots . . . . .	6 halves
Blueberries . . . . .	$\frac{2}{3}$ cup	Blueberries . . . . .	$\frac{1}{2}$ cup
Cherries . . . . .	15 large	Cherries . . . . .	$\frac{1}{2}$ cup
Grapefruit . . . . .	$\frac{1}{2}$ small	Fruit Cocktail . . . . .	$\frac{1}{2}$ cup
Grapes . . . . .	20 average	Grapefruit . . . . .	$\frac{1}{2}$ cup
Orange . . . . .	1 medium	Kadota figs . . . . .	$\frac{1}{2}$ cup
Peaches . . . . .	1 medium	Peaches . . . . .	2 halves
Pears . . . . .	1 medium	Pears . . . . .	2 halves
Pineapple, $\frac{3}{4}$ " thick . . . . .	1 slice	Pineapple . . . . .	1 slice
Strawberries . . . . .	10 large		
Prunes . . . . .	4-5 (sundried, unsulphured)	Prunes . . . . .	4
Watermelon, 6" x $1\frac{1}{2}$ " . . . . .	1 average slice		

*Fruit Juices*

(*Canned or Fresh—Check Label: No Preservative Permitted*)

Grapefruit . . . . .	8 ounces	Orange . . . . .	8 ounces
Apple . . . . .	8 ounces	Pineapple . . . . .	8 ounces
Grape . . . . .	8 ounces	Prune . . . . .	8 ounces

*Rice Recipes*

*Boiled Rice*

1 cup white rice + 2 quarts boiling water

Wash rice by placing in strainer and holding under the running cold water. Add rice gradually to boiling water so as not to stop boiling. Boil rapidly 15 to 20 minutes until tender. Drain into strainer and wash with hot water. Return rice to saucepan, place over very low heat for a few minutes.

*Broiled Rice*

2 cups cooked white rice 3 teaspoons white sugar

Place rice in 6-inch pie plate, pack down with spoon. Place in oven to broil under medium flame for 10 minutes. Rotate plate to insure even broiling. Continue to broil until upper layer of rice is well browned. Top with fruit and sugar as desired, before serving.

*Blended Fruit Cereal*

$\frac{3}{4}$  cup cooked white rice 1 small banana  
2 halves canned peaches 3 ounces syrup from canned fruit

Place ingredients in a blender. Blend to creamy consistency. Heat mixture in a saucepan. Add sugar, and serve. Other fruits may be substituted.

*Rice Pudding*

1 cup cooked white rice 1 tablespoon white sugar  
1 slice canned pineapple  $\frac{2}{3}$  cup applesauce  
1 sliced peeled raw apple

Mix rice, applesauce and sugar. Place  $\frac{1}{2}$  mixture in casserole dish greased with mineral oil. Add layer of sliced apple, then add remainder of mixture. Top with sliced pineapple. Bake at medium heat for 45 minutes.

of 2 plus or more, indicated higher chloride intake than advised and therefore, poor adherence to the diet. The cooperation of the patients was rated as: good-fair-poor on the basis of these determinations.

Improvement of symptoms, as well as a return toward normalcy of blood pressure and laboratory findings, served as a guide in the further dietary management of the individual patient. As a rule, the strict regimen was used for 6 to 8 weeks before any modifications were permitted. Occasionally, the diet had to be modified at an earlier date, e.g. when some patients with gastric hyperacidity showed intolerance to large amounts of raw fruit and canned fruit juices. In a satisfactory response, modifications were gradually permitted. The modifications were discussed with the patients, and individual likes and dislikes were taken into consideration. The additional foods were permitted in the following order: first, low sodium vegetables (cabbage, broccoli, cauliflower, tomato) beginning with amounts of approximately 2 ounces raw weight; second, potato, macaroni, unmodified oatmeal, 4 ounces cooked weight; third, lean beef or chicken, 1 to 6 ounces weekly, raw weight. The palatability of the food was improved by allowing the use of the following: pure honey, lemon juice, cider vinegar, fresh or dehydrated garlic (avoid garlic salt), and eventually 10 grams of cottonseed oil or peanut oil daily.

#### CLASSIFICATION OF PATIENTS ACCORDING TO THE DIASTOLIC BLOOD PRESSURE LEVELS

The elevation of the blood pressure represents only one manifestation of the syndrome "essential hypertension", the real nature of which remains obscure (15). This may be compared to a certain extent with the elevated blood sugar level in diabetes mellitus which also represents only one feature of a very complex disorder. Both hypertension and hyperglycemia are being used as diagnostic and therapeutic indices because they can be easily and objectively evaluated on a quantitative basis, while the other features of these disorders do not lend themselves to such an estimation. In hypertension, the evaluation of the changes in the fundi, heart, and the kidneys is more difficult and subjected to individual interpretation than that of the blood pressure level. The criteria for the evaluation of therapeutic measures on the level of the blood pressure vary considerably from author to author. In a recent publication (9) a summary of these criteria was given. In our observation, the patients were grouped into four classes according to the level of the diastolic blood pressure prior to treatment: Class I, 90-110 mm. Hg. (10 patients); Class II, 111-130 mm. Hg. (20 patients); Class III, 131-150 mm. Hg. (5 patients); Class IV, over 150 mm. Hg. (none of the patients in this study belonged to this class). We selected the level of the diastolic blood pressure as the criterion because of its greater importance and constancy.

The result of therapy was considered satisfactory if the diastolic blood pressure decreased by at least 15% of the original average pretreatment level, and if the decrease permitted regrouping of the patient to the next lower class. We consider this assessment better than that based on the decrease of 20 mm. Hg. in the mean arterial pressure, or that based upon the "trend" of the blood pressure curve. It

should be re-emphasized that this classification has been introduced by us exclusively for the comparative evaluation of therapeutic results in various groups of hypertensive individuals and by various authors. It does not pretend to be an index of the severity of the disease as such, e.g. a patient may present serious complications of eyes, heart, or kidneys, with only moderate elevation of the blood pressure.

## RESULTS

Although one had to rely for the most part on objective signs (blood pressure, body weight, chemical determinations) in evaluating therapeutic results in the syndrome of hypertension, a careful analysis of the patients' symptoms before and after treatment was attempted. For this purpose, the symptoms were arbitrarily classified under three headings: 1) cardio-vascular: dyspnea, precordial pain, and palpitation; 2) urinary tract: frequency and nocturia; 3) nervous: headache and dizziness. These symptoms were evaluated in the control period, as well as during the course of specific therapy, on a basis of 1 plus to 3 plus. Table 2 presents a summary of the observations.

Improvement was noted in the three groups of symptoms. Thus, *Palpitation* was recorded in 13 patients before, and in 6 after therapy. Severe exertional dyspnea was noted before treatment in 2 patients, and in milder degrees in 15; after therapy only 4 patients presented moderate dyspnea, in the others this symptom improved or subsided. Precordial pain was noted in 12 patients before, and in 8 after treatment. *Urinary tract symptoms*, especially nocturia, were recorded in 11 instances before and in 7 instances after therapy. It must be added that the evaluation of these symptoms in relation to the therapy employed was difficult in both sexes because of prostatic hypertrophy in the male, and cystocele in the female. The average age of the patients of the group was 57.3 years, and the interference of these mechanical factors must be taken into consideration. Because of the limited value of these symptoms, their recording was discontinued in the later observations. *Headache and dizziness* were encountered in greater frequency. Headaches were recorded in 15 patients before therapy and in 3 after therapy. Dizziness was noted in 13 patients before treatment, and in 4 after therapy. The impression was that the symptoms of headache and dizziness showed the greatest improvement. A detailed analysis of these symptoms will be found in Table 2. In addition, many patients presented general complaints such as malaise, listlessness, and easy fatigability. Some patients applied to the clinic only for the treatment of these symptoms. In the early phase of specific therapy, the general complaints not infrequently became worse, to improve later in the course of therapy. In many instances, however, fatigue remained the chief complaint throughout the treatment.

The variations of the systolic, diastolic and mean arterial pressure in Classes I to III are presented in Table 3. In Class I, 5 patients responded satisfactorily to the treatment according to our criteria. Their average diastolic blood pressure during the control period was 105 mm. Hg., and after treatment 82. This represents a drop of more than 15%, and places the patients in the next lower class



TABLE 2  
Summary of findings

NUMBER	NAME	SEX	AGE IN YEARS	DURATION OF HYPERTENSION IN YEARS	HYPERTENSION CLASS	AVERAGE BLOOD PRESSURE IN CONTROL PERIOD mm. Hg.		AVERAGE BLOOD PRESSURE LAST MONTH OF THERAPY mm. Hg.		CHANGE IN BLOOD PRESSURE mm. Hg.		BODY WEIGHT IN POUNDS				DEGREE OF COOPERATION		CARDIAC SYMPTOMS				URINARY SYMPTOMS: FREQUENCY AND NOCTURIA		NEUROLOGICAL SYMPTOMS				FUNDUS PATHOLOGY		ERG. CHANGES†	SERUM CHOLESTEROL mg./100 cc.		BLOOD UREA NITROGEN mg./100 cc.		URINE				
						Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic	Ideal	Before*	After†	Difference	Good	Fair	Poor	Palpitation	Dyspnea on Exertion	Pre-cordial Pain	Before	After	Head-ache	Dizziness	Before	After	Before	After		Before	After	Before	After		Before	After	Highest Sp. Gr. Before Therapy	Albumen
1	L. K.	M	69	2	I	200	105	196	98	-4	5	138	181	170	-11		X																		1.020	++			
2	C. F.	M	72	3	I	180	103	144	83	-36	9	147	177	140	-37		X																			1.020	++		
3	S. C.	F	55	10	I	180	110	130	82	-50	28	15	128	153	137	-16		X																		1.020	++		
4	S. R.	F	56	1	II	178	117	165	96	-13	21	11	118	197	175	-22																				1.020	++		
5	J. G.	F	68	14	I	185	102	156	94	-29	8	15	128	185	174	-11				X																1.020	++		
6	F. G.	F	66	8	II	242	128	215	115	-27	13	2	126	191	188	-3																				1.020	++		
7	E. R.	F	50	5	II	200	122	158	99	-42	23	13	128	186	139	-47																				1.020	++		
8	R. T.	F	64	10	III	230	134	156	92	-74	42	8	108	134	122	-12				X																1.020	++		
9	H. J.	F	60	2	I	185	105	180	102	-5	3	128	182	166	-16																						1.020	++	
10	L. A.	F	65	3	II	233	123	236	122	+3	1	10	116	153	144	-9				X																	1.020	±	
11	P. E.	F	58	1	II	170	116	146	88	-24	28	3	128	166	158	-8				X																1.020	±		
12	H. G.	F	60	1	II	214	120	200	113	-14	7	3	118	136	139	+3				X																1.020	±		
13	C. D.	F	41	3	II	192	122	153	90	-62	32	11	104	125	108	-17				X																1.020	±(1)		
14	L. P.	F	49	3	II	192	122	204	126	+12	4	15	106	163	150	-13				X																1.020	±		
15	E. B.	F	57	16	III	245	135	174	110	-71	25	5	118	124	107	-17				X																1.020	±		
16	M. C.	F	46	8	III	207	143	163	101	-44	42	8	131	246	216	-30				X																1.020	±		
17	B. H.	F	68	9	I	203	106	170	81	-33	25	24	138	190	162	-28				X																1.020	±		
18	C. N.	F	62	14	II	210	113	170	95	-40	18	3	135	180	175	-5				X																1.020	±		
19	M. F.	F	43	7	I	196	105	155	91	-41	14	19	148	218	200	-18				X																1.020	±		
20	M. S.	F	58	15	II	209	113	180	100	-29	13	15	131	172	169	-3				X																1.020	±		
21	S. R.	F	63	3	II	211	119	152	85	-59	34	20	141	184	160	-24				X																1.020	±		
22	G. S.	F	61	15	II	220	128	169	91	-51	37	6	125	116	110	-6				X																1.020	±		
23	P. H.	F	50	6	II	201	120	192	96	-9	24	19	131	235	221	-14				X																1.020	±		
24	M. A.	M	59	14	II	225	125	177	115	-48	10	7	168	180	163	-17				X																	1.020	±	



which in this case is the normal range. The remaining 5 patients of Class I failed to respond to therapy. Their average diastolic blood pressure fell from 105 mm. Hg. to 95 which is a difference of less than 15%. It may be stressed that the pre-treatment levels of the diastolic blood pressure were practically identical in the positive and negative reactors, while the average systolic pressure was somewhat higher in the former.

It seemed of interest to correlate the response to therapy with the degree of the patients' cooperation (table 4). In the 5 positively reacting patients, 3 were

TABLE 3  
*Variations of systolic, diastolic and mean arterial pressure in classes I to III*  
Average Figures

HYPERTENSION CLASS	TYPE OF RESPONSE TO THERAPY (PATIENT NO.)	NO. OF PATIENTS	AVERAGE SYSTOLIC BLOOD PRESSURE mm.Hg.			AVERAGE DIASTOLIC BLOOD PRESSURE mm.Hg.			AVERAGE MEAN BLOOD PRESSURE mm.Hg.		
			Pre-treatment	Post-treatment	Difference	Pre-treatment	Post-treatment	Difference	Pre-treatment	Post-treatment	Difference
I (90-110 mm. Hg.)	Positive Reactors #2, 3, 17, 29, 32.	5	200	160	-40	105	82	-23	152	121	-31
	Negative Reactors #1, 5, 9, 19, 35.	5	192	169	-23	105	95	-10	149	132	-17
II (111-130 mm. Hg.)	Positive Reactors #4, 7, 11, 13, 18, 21, 22, 23, 27, 28, 30, 31.	12	207	167	-40	120	93	-27	163	128	-35
	Negative Reactors #6, 10, 12, 14, 20, 24, 26, 33.	8	218	195	-23	121	113	-8	169	151	-18
III (131-150 mm. Hg.)	Positive Reactors #8, 15, 16.	3	227	164	-63	137	101	-36	182	133	-49
	Negative Reactors #25, 34.	2	215	210	-5	140	141	1	177	176	-1

“good”, and 2 “fair”; while in the 5 therapy resistant cases, 2 were “good”, and 3 “poor”. It was our impression that good cooperation was a factor in obtaining satisfactory therapeutic results. That this was not the only factor becomes clear if one considers that 2 patients with “good” cooperation proved to be therapy resistant.

The lowering of the blood pressure was then compared with the extent of weight loss (table 4). From the data of Class I, no conclusions could be drawn because of the small number of patients involved. The bearing of weight loss became more evident in the next class of patients.

Class II included 20 persons. The response to therapy was satisfactory in 12 (table 3). During the control period of these 12 patients, the average diastolic blood pressure was 120 mm. Hg., and after treatment 93. The average reduction of 27 mm. Hg., i.e. more than 15%, permitted reclassification of these patients from Class II to Class I. Eight patients of Class II failed to respond satisfactorily, since their average diastolic blood pressure decreased by only 8 mm. Hg., from 121 to 113 (less than 15%). Thus in our largest class of patients, 60% proved amenable to therapy according to our criteria, and 40% were refractory.

The loss of weight in Class II showed a correlation with the decrease in blood pressure. Among 12 patients whose blood pressure was reduced by therapy, 7

TABLE 4

*Blood pressure response in relation to degree of cooperation and extent of weight loss in classes I to III*

HYPERTENSION CLASS	NO. OF PA-TIENTS	NO. OF POSITIVE REACTORS	COOPERATION OF PATIENT		WEIGHT LOSS		NO. OF NEGATIVE REACTORS	COOPERATION OF PATIENT		WEIGHT LOSS	
			Pa-tients	Degree	Pa-tients	Extent		Pa-tients	Degree	Pa-tients	Extent
I (90-110 mm. Hg.)	10	5*	3	good	3	†	5	2	good	4	†
			2	fair	0	‡		0	fair	0	‡
			0	poor	2	§		3	poor	1	§
II (111-130 mm. Hg.)	20	12	4	good	7	†	8	0	good	3	†
			5	fair	3	‡		1	fair	1	‡
			3	poor	2	§		7	poor	4	§
III (131-150 mm. Hg.)	5	3	0	good	3	†	2	1	good	0	†
			2	fair	0	‡		0	fair	0	‡
			1	poor	0	§		1	poor	2	§

\* Positive Reactors: At least 15% decrease in pretreatment diastolic blood pressure with a shift to a lower class.

† Indicates weight loss of more than 10 lbs.

‡ Indicates weight loss of 5-9 lbs.

§ Indicates weight loss of less than 5 lbs.

lost 10 pounds or more of body weight, 4 lost 5 to 9 lbs. and 1 less than 5 lbs. In contrast, among the 8 patients whose blood pressure level failed to respond to therapy, 3 lost 10 lbs. or more, 1 lost 9 lbs., 3 less than 5 lbs., and 1 gained 3 lbs. Hence there was greater weight reduction among the "positive reactors" which is in agreement with the well established effect of weight reduction upon hypertension (1, 3).

The relationship between response to therapy and degree of patients' cooperation was as follows: of the 12 "positive reactors" of Class II, 4 were "good", 5 "fair", and 3 "poor"; of the 8 refractory patients, 1 was "fair", and 7 were "poor". The cooperation of the patient apparently contributed to the final result of diet therapy in Class II.

Class III consisted of 5 patients, 3 of whom responded to therapy and 2 did



not. The former showed a drop in the average diastolic blood pressure of 36 mm. Hg. (137 to 101), while the latter showed no change (140 to 141). No conclusions could be drawn concerning the cooperation of the patients in this class. In regard to weight reduction, the 3 patients whose blood pressure responded to therapy lost 10 lbs. or more each, while a loss of zero and 3 lbs. respectively was noted in the 2 therapy resistant persons.

It was of interest to compare the variations of systolic and diastolic blood pressure with those of the mean arterial pressure as they occurred during therapy (table 3). It is evident that the positive reactors were sharply differentiated from the negative ones by changes in the systolic and diastolic blood pressure, as well as in the mean arterial pressure. In Classes I and III the differences between the positive and negative reactors are more pronounced in the systolic and mean blood pressure than in the diastolic. In Class II, however, which includes the largest group of patients, these differences were not significant. Although in Classes I and III, the differences are comparatively smaller in the diastolic blood pressure than in the systolic and mean, they are of greater significance because of the comparative stability and greater diagnostic and prognostic importance of the diastolic blood pressure.

The other data (summarized in table 2) do not contribute essentially to the objective evaluation of the results. The patients of this group were in the benign phase of hypertension with one exception. The encountered pathological changes in the fundi were of a mild degree. Only 1 patient presented hemorrhages and exudates of the fundi, 2 marked tortuosity, narrowing of the vessels and arteriovenous compression, and 8 had similar changes of a milder degree. In the course of therapy, no changes of the fundi were seen. It should be added, however, that patient #34, with chronic glomerulonephritis who presented the severest changes of the fundi, failed to respond to therapy during a period of 2 months. At that time treatment was discontinued because of gastro-intestinal hemorrhage from a preexisting duodenal ulcer.

Six patients presented electrocardiographic evidence of myocardial damage 1 had similar changes and bundle branch block, and 1 had evidence of an old coronary occlusion. No statement can be made on the effect of the diet on these changes.

Only 2 items of the blood chemistry were of interest. The serum cholesterol was examined during the control period in 16 patients and ranged between 240 and 600 mg. per 100 cc. After therapy, 2 patients showed a marked drop of serum cholesterol from 600 and 580 to 360 and 320 mg. per 100 cc. respectively, while 1 patient showed an increase from 240 to 340 mg. It is thus evident that a number of the patients presented hypercholesterolemia, and that a decrease to lower cholesterol levels may be observed under therapy (8).

The urea nitrogen content of the blood was determined during the control period in 18 patients. It ranged from 7 to 36 mg. per 100 cc., average 14.3. Only 2 patients presented abnormal values of 30 and 36 mg. respectively. In these 2 instances, there was a lowering of the levels during therapy to 9 and 22 mg. per 100 cc., respectively.

The Fishberg concentration test was performed in 14 patients during the control period. The highest specific gravity of the urine varied from 1.010 to 1.030, average 1.022. Only 1 patient with chronic nephritis (#34) showed fixation of specific gravity, while the others showed the usual variations.

#### DISCUSSION

The experience with the rice diet in this group may be summarized as follows: of 35 patients, 20 (57%) responded favorably with lowering of the diastolic blood pressure levels according to our criteria, and 15 (43%) were therapeutic failures. It must be stressed that all patients had been treated during the control period of at least 6 months before diet therapy was initiated. Only those whose blood pressure remained stabilized at an elevated level were included in the group. This study was performed on an ambulatory group of patients from the lowest income brackets and from City Welfare Rolls. The results are indicative of what was achieved with the rice diet over a prolonged period of time (average 10.3 months) under most difficult social and economic conditions.

The majority of the patients showed a marked improvement of symptoms, especially headache, dizziness and exertional dyspnea. The impression was that the early improvement of symptoms was attributable to salt and water loss, and later to this factor as well as to the lowering of blood pressure. The cooperation of the patients and loss of weight proved to be important factors in obtaining satisfactory results. The patients remained ambulatory and active throughout the treatment and psychological effects of enforced inactivity were avoided.

The regime presented of course great inconvenience and severe limitation in the patients' daily life. The basic rice diet was found to be inadequate in protein, fat, blood building materials, minerals (iron) and vitamins (8, 13, 14). It was also most difficult to achieve satisfactory caloric intake, although theoretically the caloric value of the diet was unlimited. Many patients made a good adjustment to the deficiencies of the diet, especially when later in the course of the treatment modifications were permitted, and moderate amounts of protein and fat were added. Supplementary vitamin concentrates and iron preparations were prescribed from the start. It required time, good will, patience and persistence on the part of both patient and physician to achieve a satisfactory physical and psychological adjustment of the patient. In our experience optimal physician-patient relationship was a prerequisite for achieving this result. Despite all efforts, a considerable group of patients were unable to make a satisfactory adjustment to the diet and eventually rejected it. The original group of patients was thus reduced to 35 and others had to be placed on less restricted types of low sodium diet.

Untoward effects of salt depletion as they were observed by others (10, 13) were not encountered in our group of patients. This was probably due to the fact that with one exception, they presented normal renal function, and that no additional salt depleting measures, like mercurial diuretics were used. In one patient a severe gastro-intestinal hemorrhage occurred from an old duodenal ulcer. Although no conclusion can be drawn from a single observation, consider-

able difficulties were encountered with the rice diet in the management of patients with gastric hyperacidity without peptic ulcer. In several instances the use of large quantities of raw fruit and fruit juices aggravated the gastric symptoms and necessitated a change of the regime and the use of salt free milk. Patients with peptic ulcer, when on the rice diet, require special supervision.

Much has been written on the mode of action of the rice diet (5-9). The extreme limitation of sodium is certainly an outstanding feature of the regime, and there is evidence that its effect upon hypertension may be exerted through the adrenal cortex (12). One is inclined to believe that the other characteristics of the diet, e.g. its low content of protein, fat, cholesterol and even calories, should not be neglected. The loss of weight might have exerted blood pressure lowering effect *per se* (1, 3). Undoubtedly psychological factors contributed greatly to the results. The steady interest of the physician manifesting itself in frequent examinations, blood pressure readings, and in long interviews centering around the patient's health and well-being as well as extreme limitation of the regime were important psychological factors. In the majority of the patients, an increased feeling of security was observed. A small group however responded with increased anxiety and apprehension and these patients were among the failures. The importance of optimal physician-patient rapport was already stressed.

Our observations are in agreement with the results of some other workers in the field (5, 9, 11). However they differ from the results of Landowne, et al (8A) who, in a very carefully arranged study on low sodium diets, failed to observe any noteworthy blood pressure lowering effects. This difference may be explained by the following facts: 1) Landowne employed diets with higher protein and sodium content than those employed by Kempner, 2) Landowne et al used the dietary regime for only 6 weeks, while the average duration of treatment in this study was 10.3 months, 3) Landowne et al carefully avoided loss of weight, while in this group of patients loss of weight was present.

Is the use of a severely restricted diet such as the rice diet, justified for the treatment of arterial hypertension? At present, the consensus of opinion favors extreme limitation of salt and protein in *malignant* hypertension, especially when heart failure, advancing retinopathy and renal insufficiency threaten life. The rice diet combines extreme protein and salt limitation. Its use in *benign* hypertension however requires extensive additional study. The results of our observations do not permit general conclusions, because of the comparatively small number of the group. In our opinion the use of extreme dietary limitation of the type of the Kempner diet will be justified for the treatment of benign hypertension only, if evidence will become available that the transition into the malignant phase can be prevented and that prolongation of the life span of the hypertensive can be achieved. This question cannot be answered at present. Many years of careful observation will be necessary to solve this problem on an adequate statistical basis.

#### SUMMARY

1. The rice diet was employed during a period of 2 to 24 months, average 10.3 months, in a selected group of 35 clinic patients of a large general hospital.

Thirty four had hypertensive vascular disease in the benign phase, and one chronic nephritis.

2. The patients were divided into four classes according to the diastolic blood pressure which had been recorded during a control period of at least 6 months. Only persons whose blood pressure remained stabilized during the control period were included in the study.

3. The effect upon the blood pressure was evaluated in this controlled study by a special formula based on the lowering of the diastolic blood pressure. According to this criterion, twenty patients (57%) responded favorably, and fifteen (43%) proved to be failures.

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## A SIMPLE TEST FOR EXTENT OF SYMPATHECTOMY\*

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The widespread use of surgery of the autonomic nervous system makes a simple test for extent of sympathectomy desirable. This is especially true if the late results of operation are to be properly evaluated.

The tests now generally employed are based mainly on the autonomic innervation of the sweat glands. Interruption of the outflow of the thoracic and lumbar divisions of the autonomic system, as is well known, abolishes thermoregulatory sweating in the skin of the denervated area. The clinical methods now available demonstrate this localized loss of sweating either by a color reaction such as Minor's iodine starch test, or measure galvanic skin resistance. In either instance generalized sweating is first induced by heating the patient in a hot air cabinet, under a heat cradle, by the use of hot tea and aspirin, or by the parenteral administration of drugs such as pilocarpine or mecholyl.

It would seem that a simple method, more easily applied at the bedside, should be useful.

*Rationale of Proposed Test.* The method to be described is also based on the sympathetic control of the sweat glands. The local injection of parasympathomimetic drugs into the skin causes local sweating. The degeneration of sympathetic nerve fibers following post-ganglionic sympathectomy abolishes this response. This effect has been demonstrated by Kahn and Rothman (1) for the intracutaneous injections of acetylcholine and mecholyl in male patients. These authors found that female patients did not usually respond to the dosage of acetylcholine which they employed (0.12 cc. of a 1:1000 solution). By using solutions with higher acetylcholine concentration (0.1 cc. of 1:10 to 1:500) we have been able to extend their observations to females.

Furthermore, we have been able to show that the local sweating induced by the intracutaneous injection of pilocarpine, prostigmine, and eserine likewise disappears following post-ganglionic sympathectomy in males and females.

Thus, the local sweating induced by acetylcholine (0.1 cc. of 1:10 solution), or pilocarpine (0.1 cc. of 1:1000) was noted to disappear in four patients following unilateral lumbar sympathectomy for peripheral vascular disease at 30, 38, 48 hours, and 7 days respectively, following operation. These patients were followed daily from operation, and the limb on the side which was not operated upon served as a control from which a normal sweating response was elicited.

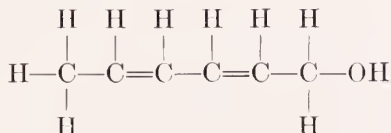
Five other patients were studied for the first time at various intervals following operation, and were found to have no local sweating response to these drugs in the denervated areas at periods of from three days to seven months following their operations. Three had bilateral thoracico-lumbar sympathectomy

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for essential hypertension, two had unilateral lumbar sympathectomy for peripheral vascular disease.

*Proposed Test.* The clinical application of these facts has been considerably simplified by the recent introduction of a new substance, *hexadienol*<sup>1</sup>, which causes localized sweating when applied to the skin by inunction. This material, a diene alcohol of the form  $C_nH_{2n-3}OH$ , has had the formula  $C_6H_9OH$ , and the following structure proposed for it:



Koppanyi (2) has shown that it has no toxic side effects, is free of generalized parasympathetic stimulation, and that it has a direct muscarinic effect on sweat glands.

We have observed that this local sweating response is abolished following post-ganglionic sympathectomy. Thus the simple application of this material by inunction will cause sweating in innervated areas, and will fail to cause sweating in denervated areas.

*Technique of the Test.* Sweating is easily demonstrated by the method of Silverman and Powell (3).

1. The area of skin to be tested is painted with ordinary tincture of ferric chloride (U.S.P.) diluted 1:3 with alcohol, using a cotton applicator. This dries quickly leaving the skin a light yellow color.

2. Hexadienol, (the pure chemical is a semisolid ointment) is applied to this area, and rubbed into the skin for at least a minute. The excess is wiped off.

3. The area is then lightly dusted with tannic acid powder. A powder dispensing box, with perforated top, or an atomizer may be used.

4. Sweating is detected by the appearance of discrete black spots at the mouths of the sweat glands in normal skin within from 5 to 20 minutes, usually 5 to 10 minutes.

5. The black ink which is formed is removed with 5 per cent oxalic acid. The hexadienol sweating is stopped by cleansing with alcohol.

*Application of Test.* We have tested ten patients with this method. Two had unilateral lumbar sympathectomy for peripheral vascular disease, eight had bilateral thoracico-lumbar operations for essential hypertension.

The two patients with unilateral lumbar sympathectomy were followed daily from the time of operation, and hexadienol induced sweating disappeared in the denervated areas in 30 and 48 hours respectively, following operation.

The eight hypertensive patients were tested at various intervals following operation and found to have no response to hexadienol applied locally to the denervated areas at three days, and three months for one; four months, and

<sup>1</sup> Obtained through the courtesy of Dr. Theodore Koppanyi, Georgetown University School of Medicine, Washington, D. C. Hexadienol is manufactured by the Consolidated Chemical Company, Cleveland, under the trade name *Hexene-ol*.

five months for the second; 24 days, and seven months for the third; and three to eighteen months for the remaining five.

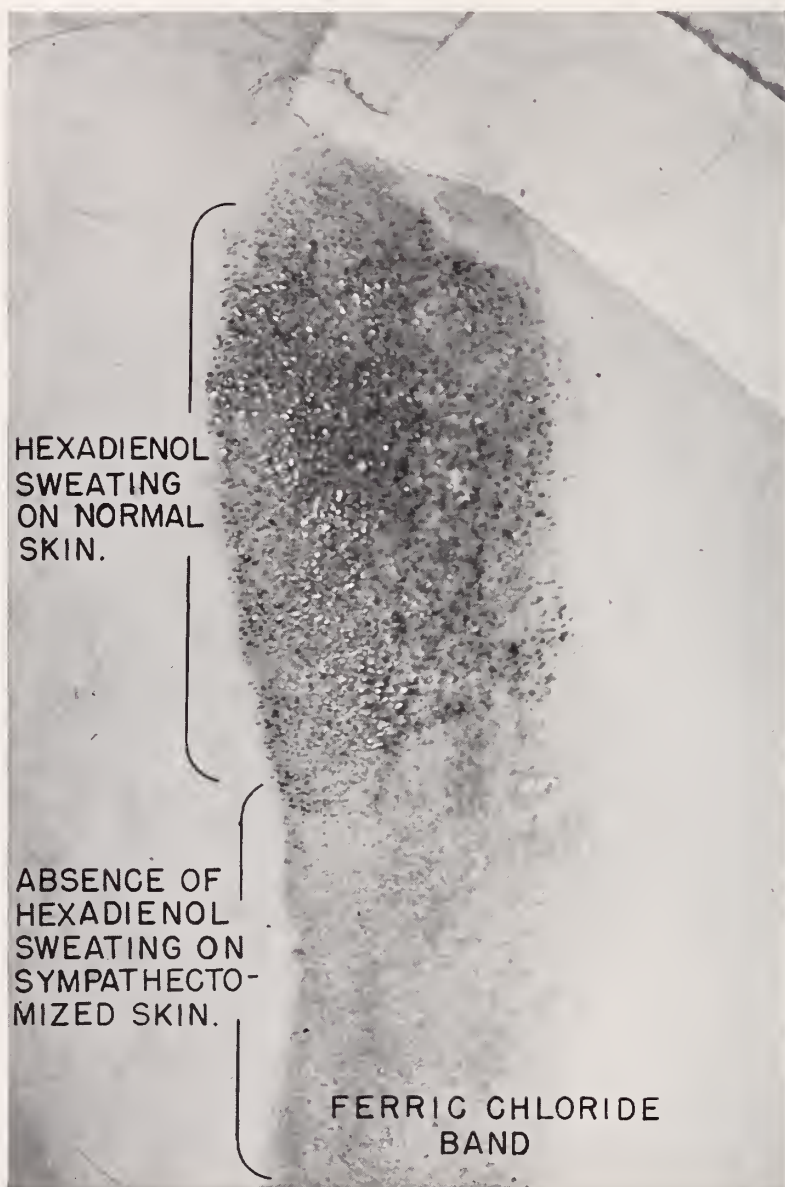


FIG. 1. Patient three days following thoracic post-ganglionic sympathectomy. Hexadienol induced sweating of the intact skin; it failed to induce sweating in denervated skin.

We have found it convenient to paint a wide band of the skin along the trunk or thigh, covering several adjacent dermatomes when we have been interested in mapping out the limits of a denervated area. The boundary between de-

nervated and innervated areas is sharply demarcated by this method. (See fig. 1). In every case, an area of innervated skin is anointed and caused to sweat to serve as a control.

#### SUMMARY

1. The local sweating which is caused by the application to the skin of parasympathomimetic drugs, and which disappears after post-ganglionic sympathectomy offers a pharmacological rationale for testing the extent of sympathetic denervation.

2. A simple test, based on this rationale, and employing the local use of *hexadienol* is described.

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## THE ROLE OF ACCESSORY SPLEENS IN POST-SPLENECTOMY RECURRENT PURPURA HEMORRHAGICA

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One of the first splenectomies performed for purpura in this country was done by Dr. A. A. Berg in 1921. The patient made an uneventful recovery and is alive and well after nearly thirty years. Such good results are now the rule in this disease, but a few patients fail to respond to the operation.

From a series of cases of idiopathic thrombocytopenic purpura treated by splenectomy over a period of twenty nine years, fourteen failures have recently come to our attention. It is the purpose of this communication to evaluate this experience with respect to the role of accessory spleens. The case histories of four of these are to be recorded in detail; the others are presented only in summary (tables I and II). Hematologic data are shown in Tables III and IV. In all of the cases, when first seen, and at subsequent visits when in relapse, the findings were typical of the disease. There was thrombocytopenia, prolongation of bleeding time and absence of clot retraction. In addition, bone marrow aspiration was normal except for lack of platelet formation by megakaryocytes. These cases represent a cross-section of purpura patients. Eleven were female, three male. Most were in the third and fourth decades of life when first struck by the disease, but two had had onset in childhood and one at the age of sixty-five. Nothing in the histories or in the physical or hematologic findings could serve to set them aside as cases which might be expected not to benefit from splenectomy.

In twelve of the fourteen cases there is good evidence of the presence or absence of accessory spleens. Following a suggestion of Doan (1), we attempted visualization of accessory splenic tissue by means of thorotrast (2) in seven patients.<sup>1</sup> Exploratory laparotomies were done in six cases, and post-mortem examinations in three.

In four cases two of these procedures were performed. Positive thorotrast x-rays were confirmed at laparotomy in two cases; in a third, the thorotrast film was questionable, and laparotomy failed to reveal an accessory spleen. The fourth was a patient in whom an accessory spleen was not found at laparotomy, but who proved later, on post-mortem examination, to have one.

Although when first seen these fourteen cases formed a homogenous collection, their subsequent courses separated them into two distinct groups. Group I (table I, cases 1-8) includes the eight patients who, following splenectomy, experienced true remissions with both clinical and hematologic improvement. All these patients later relapsed. Group II (table II, Cases 9-14) consists of six patients whose diseases were apparently entirely unaffected by splenectomy.

<sup>1</sup> Thorotrast was used in a modification of the method of Yater and Otell. After a preliminary x-ray film of the abdomen had been taken, 18 cc. (4.5 grams) of a 25 per cent aqueous suspension of thorium dioxide (thorotrast) was administered intravenously on each of two successive days. Twenty-four to forty-eight hours after the second dose, another abdominal x-ray was made.

TABLE I

CASE NO.	ON- SET AGE	SEX	DURATION BEFORE SPLENEC- TOMY	REMISSION FOLLOWING SPLENEC- TOMY	ACCESSORY SPLEEN	HOW DEM- ONSTRATED	ACCESSORY SPLENECTOMY	REMISSION FOLLOWING ACCESSORY SPLENECTOMY	SUBSEQUENT COURSE
1. R. D.	8 <i>yrs.</i>	F	3 mos.	12 yrs.	yes	Opera- tion	yes	1 yr.	Well 1 year after accessory sple- nectomy, 21 yrs. after splenec- tomy
2. M. P.	24	F	5 yrs.	14 mos.	no	Post- mor- tem	—	—	Death from pur- pura 16 mos. after splenec- tomy
3. L. W.	1	M	18 mos.	2 yrs.	?	—	—	—	Intermittent bleeding—living 8 yrs. after splenectomy
4. B. Gr.	27	F	18 mos.	12 days	yes	Thor- o- trast and Oper- ation	yes	10 days	Intermittent bleeding—living 4 mos. after ae- cessory splenec- tomy, 16 yrs. after splenec- tomy
5. I. Al.	23	M	3 yrs.	8 mos.	yes	Thor- o- trast and Oper- ation	yes	5 mos. +	Well 5 mos. after accessory splenectomy, 6 yrs. after splenectomy
6. B. Go.	36	F	2 yrs.	3 yrs.	no	Thor- o- trast and Oper- ation	—	—	Bleeding—living 4 yrs. after splenectomy
7. J. Gr.	38	F	3 yrs.	2 mos.	?	—	—	—	Intermittent bleeding—living 2 yrs. after splenectomy
8. C. II.	27	F	3 yrs.	12 yrs.	no	Thor- o- trast	—	—	Death from pur- pura 13 yrs. after splenectomy

Some of these did have partial clinical remissions, but in none did the platelet count ever return to normal.

TABLE II

CASE NO.	ON- SET AGE	SEX	DURATION BEFORE SPLENEC- TOMY	REMIS- SION FOL- LOWING SPLE- NEC- TOMY	ACCESSORY SPLEEN	HOW DEMON- STRATED	ACCESSORY SPLE- NEC- TOMY	REMIS- SION FOL- LOWING ACCESSORY SPLE- NEC- TOMY	SUBSEQUENT COURSE
	<i>yrs.</i>								
9. S. Sh.	65	F	2 mos.	none	no	Thorotrast	—	—	Death from purpura 5 yrs. after splenec- tomy.
10. M. R.	56	F	3 mos.	none	no	Thorotrast	—	—	Death from purpura 18 mos. after splenectomy
11. B. Ar.	41	F	2 mos.	none	no	Thorotrast	—	—	Bleeding—living 1 yr. after splenectomy
12. F. F.	30	F	18 mos.	none	no	Operation	—	—	Death from purpura 18 mos. after splenectomy
13. H. L.	16	M	2 yrs.	none	no	Postmor- tem	—	—	Death from purpura 4 yrs. after splenec- tomy
14. H. Si.	28	F	1 yr.	none	yes	Postmor- tem	—*	—	Death from purpura 6 yrs. after splenec- tomy

\* Attempted, not found.

TABLE III  
*Hematologic data (initial)*

CASE NO.	HEMO- GLOBIN (per cent)	RED BLOOD CELLS ( $\times 10^6$ )	WHITE BLOOD CELLS ( $\times 10^3$ )	DIFFERENTIAL	PLATE- LETS ( $\times 10^3$ )	BLEEDING TIME (minutes)	COAG- ULA- TION TIME (min- utes)	TOURNI- QUET TEST	CLOT RE- TRACTION
1. R. D.	90	4.00	15.0	Normal	15	Indef.		+	
2. M. P.	48	4.25	9.4	"	35	22'	25'	+	None
3. L. W.	76	5.14	7.0	"	40	27	10	—	Slight
4. B. Gr.	66	4.06	5.8	"	40	20	8	+	None
5. I. A.	69	3.50	16.2	"	5	10	17	+	"
6. B. G.	76	4.06	10.6	"	5	20	8	+	"
7. J. Gr.	83	4.56	12.9	"	10	20	6	+	"
8. C. H.	71	4.16	10.8	"	20	5	4	+	"
9. S. Su.	74	4.70	5.4	"	10	17+	12	+	"
10. M. R.	76	4.49	6.4	"	30	15	8	+	"
11. B. Ar.	87	4.49	8.8	"	20	20	5	+	"
12. F. F.	32	1.99	6.1	"	5				
13. H. L.	26	1.60	7.1	Neutropenia lymphocytosis	15				
14. H. S.	40	2.53	7.1	Normal	5	45+	25	+	"

## CASE REPORTS

Of the eight cases in Group I (patients having true remissions), the case histories of three are being presented in detail, as illustrations of the extreme variability with regard to the presence and importance of accessory spleens.

*Case 1. (R.D.)* A girl aged eight years was first admitted to The Mount Sinai Hospital on October 21, 1929 under the care of Dr. Reuben Ottenberg. She had had measles, whooping cough and mumps. Her recent illness started in September of 1929 when she returned from camp and her family noticed ecchymotic spots spread diffusely throughout the skin. She

TABLE IV  
*Bone Marrow Examinations*

CASE NO.	TIME	TOTAL NUCLEATED CELLS	MEGAKARYOCYTES	COMMENT ON MEGAKARYOCYTES	DIFFERENTIAL
1. R. D.	Post-splenectomy	210,000	154	Maturation arrest, platelet formation diminished	Normal
3. L. W.	Pre-splenectomy	500,000	330	Marked immaturity	"
5. I. A.	Pre-splenectomy	165,000	11	Maturation arrest	"
6. B. Go.	Post-splenectomy	122,000	110	Maturation arrest some platelet formation	"
7. J. Gr.	Pre-splenectomy	323,000	198	Maturation arrest platelet formation diminished	"
8. C. H.	Post-splenectomy	149,000	66	Platelet formation diminished	"
9. S. Sh.	Pre-splenectomy	90,000	154	Maturation arrest little platelet formation	"
10. M. R.	Pre-splenectomy	46,000	154	No platelet formation	"
14. H. S.	Post-splenectomy	75,000	44	Little platelet formation	"

Cases 2, 4, 12 and 13 were under observation before bone marrow observations were performed.

Case 11, bone marrow was performed in another hospital and reported as normal.

was bleeding from the gums and nose. For two or three months she had had occasional attacks of epistaxis. Following an attack of hematuria she was given several transfusions. During this episode of bleeding she had had some irregular temperature. On admission, physical examination revealed petechial hemorrhages scattered all over the body with large ecchymotic spots on the extremities and on the trunk. There was a large subconjunctival hemorrhage in the right eye. The heart and lungs were normal. Spleen was felt one finger below the costal margin. The blood findings revealed: hemoglobin, 90 per cent; red blood cells, 4,000,000; platelet count, 15,000. The bleeding time was markedly prolonged. The blood smear showed no abnormality. Urinalysis was negative. On Novem-



ber 18, 1929 splenectomy was performed by Dr. A. A. Berg. Spleen was found to be free of adhesions and appeared moderately enlarged. No accessory spleens were found. The pathologist reported, "moderate hyperplasia of reticulum cells with hyalinization of blood vessels. No evidence of platelets". Frequent platelet counts were done by Dr. Ottenberg. The counts varied from 200,000 to 420,000 per cmm. during the year following operation.

The patient was well for ten years but noted some bruising while at college. After graduation in 1941, she became a student nurse at The Mount Sinai Hospital. Because of her prolonged menstrual periods, numerous ecchymotic areas and easy bruising she was examined and found to have thrombocytopenic purpura. She was advised to discontinue training. In 1941 because of a profuse menorrhagia she had a curettage following which she showed marked improvement.

She was readmitted on October 30, 1943 because of a recurrence of menorrhagia and gastrointestinal bleeding. For three days previous to admission she had had abdominal distention. Physical examination at this time revealed a well developed, pale female with bruised lips and numerous ecchymotic spots. The blood pressure was 130 systolic and 80 diastolic; pulse, 120; temperature, normal. There was moderate periumbilical tenderness. Investigation to determine if there was any contributing pelvic lesion proved negative. The blood findings at this time were as follows: hemoglobin, 50 per cent; red blood cells, 3,200,000; white blood cells, 26,000; platelets, 10,000; polymorphonuclear neutrophils, 68 per cent. Except for a slight polynucleosis the differential was normal. Bleeding time was 11 minutes, coagulation time 12 minutes, tourniquet test positive, clot retraction none in 26 hours.

#### *Sternal Marrow Aspiration*

Total nucleated count:.....	210,000 per cubic millimeter
Megakaryocytes:.....	154 per cubic millimeter

	per cent
Myeloblasts.....	2.0
Myelocytes.....	29.0
Myelocytes, eosinophilic.....	1.6
Polymorphonuclear neutrophils, nonsegmented.....	27.3
Polymorphonuclear neutrophils, segmented.....	7.3
Polymorphonuclear eosinophils.....	2.3
Hematogones.....	2.6
Lymphocytes.....	3.3
Plasma cells.....	0.3
Reticulum cells.....	0.3
Erythroblasts.....	1.0
Normoblasts.....	23.0

Differential essentially normal. Megakaryocytes show arrest of maturation with little or no platelet formation.

Prothrombin index 100 per cent. The other laboratory findings were non-contributory. The patient continued to have uterine bleeding and was transfused several times. There was a rise in hemoglobin and red cells but the platelets remained at 10,000 per cubic millimeter. The bleeding subsided and Parathormone was given in the hospital and continued under the supervision of her physician. There were two subsequent readmissions because of marked bleeding from the gums. These episodes became more marked just before and during menstrual periods. She received numerous transfusions to replace blood loss and to help stop the hemorrhagic tendency. During this fourth admission, in spite of repeated transfusions, the marked anemia continued (hemoglobin, 39 per cent; red blood cells, 2,200,000; white blood cells, 13,000; platelets, 10,000). The possibility of the presence of accessory spleens was entertained and possible surgical therapy was considered. Because of her poor condition, the surgical consultant advised against intervention at this time.

After several weeks gradual improvement was noted and the patient was discharged and continued under the care of one of us (P.V.).

She resumed limited activities but still had marked bleeding at her menstrual periods. After several months the anemia became quite pronounced and she was admitted to The New York Hospital. At this time the blood count was as follows: hemoglobin, 43.5 per cent; red blood cells, 2,850,000; white blood cells 11,500; platelets, 20,000, with a shift to the left in the differential. Bleeding time was more than 18 minutes, clotting time, 9 minutes, Flick test, positive; clot retraction, none. The patient was placed on citrus pectin, 2 grams 3 times a day by mouth. In addition, numerous transfusions were given. On improvement she was discharged.

While at home she continued to have profuse menstrual periods and marked bleeding from the gums and on October 8, 1944 was readmitted to The New York Hospital because of cerebral hemorrhage with right sided weakness and difficulty with speech. On the day

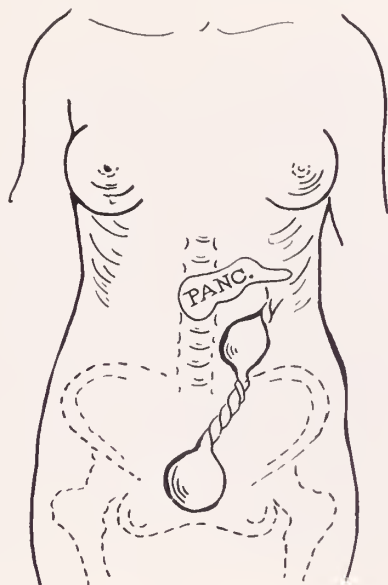


FIG. 1. Diagrammatic sketch showing twisting of pedicles of accessory spleens causing auto-splenectomy.

following admission she became semi-stuporous and was unable to move her right side. After a few weeks she began to show slow but steady improvement. She was given 50 milligrams of testosterone propionate daily to control vaginal bleeding and x-ray sterilization was started to prevent further complications from uterine bleeding. Following irradiation to the ovaries the menstrual periods were abolished. She was seen in the office at frequent intervals and numerous blood examinations from 1944 to 1949 showed the platelets usually around 10,000 to 20,000. Only at one time was there a rise to 70,000. During this time the patient felt fairly well and had no bleeding from the mucous membranes but did have occasional ecchymotic areas. She married and moved to Baltimore but returned for periodic examinations. In June 1949 she had abdominal pain of two days duration and was admitted to a Baltimore Hospital on June 22, where she was observed for a surgical abdomen. Because of her past history one of us (P.V.) was consulted and was kept informed as to the patient's condition. On the day after admission, which was the third day of illness, the platelet count was 400,000. Three days following admission the platelet count rose to 650,000. Because of a pelvic mass which was corroborated by two

gynecological consultants who thought it was a twisted solid tumor of the ovary, a laparotomy was performed on the fourth day after admission. The following is the surgeon's<sup>2</sup> description of the findings:

"On going into the abdomen there was a mass the size of a grapefruit wedged in the cul-de-sac behind the uterus. The mass was definitely infarcted and on freeing it, it was found to have a pedicle going up toward the left upper quadrant at about mid-way (fig. 1). At about mid-line there was another semi-solid infarcted organ which when freed, was also found to be attached to an area near the tail of the pancreas. The pedicle then fanned out into the peritoneum, the pedicle was clamped and doubly ligated at this point. On examination these specimens were definitely infarcted spleens with twisted pedicles. A thorough exploration of the abdomen was made for further accessory spleens but none were found."

Two days post-operative, the platelet count rose to 1,700,000 and the patient was discharged on the fifth post-operative day. Since operation she has had a number of blood examinations all of which were normal. The following is typical of the findings since the operation for removal of the accessory spleens:

8/17/49

Hemoglobin	92 per cent
Red blood cells	4,740,000
White blood cells	9,000
Platelets	370,000
Reticulocytes	<0.5 per cent

Nonsegmented neutrophils	4 per cent
Segmented neutrophils	56 per cent
Eosinophils	1 per cent
Lymphocytes	34 per cent
Monocytes	4 per cent
Myelocytes	1 per cent

Hematocrit	47 per cent
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Bleeding time	3 minutes
Coagulation time	9 minutes (Lee and White)
Clot retraction	present

Pinch test	slightly positive
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Tourniquet test	negative
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Prothrombin time	11 seconds
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10% prothrombin time	21 seconds (135%)
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Serum prothrombin time	34 seconds (91% prothrombin consumption)
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Re-examination a few weeks before this writing showed continued normal findings.

*Comment:* The implication of this case seems clear. A child of eight developed chronic thrombocytopenic purpura. Splenectomy was performed and she recovered promptly with rise of platelets to normal levels. Ten years later purpura recurred, and persisted for eight years; during this period she was desperately ill several times. She then developed an acute abdominal condition, at which time her platelet count rose to normal levels. Operation disclosed infarction of two accessory spleens, which had apparently had long pedicles. Following this self-performed splenectomy she was cured of her purpura and has remained well

<sup>2</sup> We are indebted to Dr. E. Berman for description of operative findings.

for one year. Her blood findings have returned to normal. Here the accessory spleens must be assumed to have been a major factor in the recurrence of purpura hemorrhagica.

The next case record is less clear.

*Case 4. (B. Gr.)* A housewife aged 29 years, presented herself in May 1934, because of bleeding from vagina, mouth and nose of one and one-half years duration. Physical examination showed evidence of a hemorrhagic diathesis; the spleen was just palpable at the costal margin. Hematologic findings were typical of idiopathic thrombocytopenic purpura (table I).

A splenectomy was performed on May 19, 1934 by Dr. A. A. Berg. Immediately after operation there was cessation of spontaneous bleeding. The platelets gradually rose, reaching normal (210,000) by the fifth post-operative day. This remission was extremely short-lived, and twelve days after operation the catamenia began, and at the same time there



FIG. 2.



FIG. 3.

was onset of oral bleeding and showers of petechiae over the extremities. Platelet count dropped to 50,000.

During the next fifteen years there was intermittent purpura, sometimes, but not always in relation to menstruation. Platelet counts were usually low, especially in relation to episodes of bleeding, but occasionally reached low normal values, (10,000 to 80,000 with rare count up to 130,000). She was able to continue her activities except when bleeding was severe.

In May 1949 she was re-investigated with the aid of thorotrast. X-ray films are shown in Figures 2 and 3; report was as follows:

"Examination of the abdomen before and after the injection of thorotrast shows opacification of the liver. In addition there is an apparent opacification of a round mass in the left upper quadrant measuring about  $3\frac{1}{2}$  cm. in diameter. This could represent an accessory spleen."

Abdominal exploration was advised. The patient preferred to delay the procedure but finally on Jan. 17, 1950 laparotomy was performed by Dr. A. W. S. Touroff. An accessory spleen about 3 cm. in diameter was found and removed. Pathological report read:



"Accessory spleen showing no significant change except presence of iron pigment." After this operation there was a prompt clinical and hematologic response. Platelets rose to normal by the fifth post-operative day. Ten days later, however, showers of petechiae began to appear, and the platelets were again found to be markedly reduced (20,000). At the present time (June 1950) the patient continues to have mild purpura, with thrombocytopenia of 20,000. There has been little change in the clinical status.

*Comment:* In this case, although an accessory spleen was found, its removal caused only a temporary improvement in symptoms and blood picture. In retrospect, its presence cannot be considered to have played any important role in the thrombocytopenia.

*Case 6. (B. Go.)* A housewife aged 37 years was first seen on February 24, 1946, because of purpura of one year's duration. Hematological findings were typical of purpura hemorrhagica (table I). Splenectomy was performed on March 2, 1946 by Dr. L. Colp. Although bleeding stopped after the operation, platelets did not rise until two weeks later, when they attained a level of 240,000. She remained well, and subsequent platelet counts were normal, until July 1949, when purpura recurred. Platelet count then was 60,000. Since then bleeding has varied in intensity from time to time but thrombocytopenia has been constant, with values ranging from 10,000 to 70,000. In May 1950 a search was made for accessory splenic tissue by means of Thorotrast.

X-ray report:

"Examination of the abdomen, after injection of thorotrast, shows the liver to be opacified. In addition there is opacification of a large mass in the left upper quadrant, measuring about 12 cm. in diameter. It is difficult to differentiate between an unusually shaped left lobe of the liver and a large accessory spleen." (fig. 4).

Exploratory laparotomy showed the mass to be hepatic tissue; an extensive search failed to reveal any accessory spleen. The patient recovered promptly from this operation, but still has purpura, and her platelet count is unchanged.

*Comment:* Here is a patient whose history of purpura, splenectomy, apparent cure and later recurrence follows closely the pattern laid down in the report first presented. Yet thorotrast, plus a most careful and extensive exploration, failed to reveal any accessory spleen. A left upper quadrant mass outlined by thorium was found at operation to be the left lobe of the liver. It is, of course, possible that a small accessory spleen could be overlooked in an abdominal exploration (Case 14 below). However, no such small mass was opacified by thorotrast, and the combined evidence of the two search methods seems fairly conclusive.

The remaining patients in this group had similar histories. Duration of post-splenectomy remissions varied (table I), but such remissions were present in all eight cases. Two of the eight (Cases 3 and 7) have not yet been studied with Thorotrast or by laparotomy. Three of the remaining six have had accessory spleens; three had not. Of the three in whom accessory spleens were found, two have already been presented (Cases 1 and 4). The third (Case 5) was well when last seen, 5 months after accessory splenectomy. His platelet count had fallen, to 130,000.

Attempts to draw conclusions from small series of cases are always fraught with danger. However, this much seems clear. Of patients with purpura hemorrhagica apparently cured by splenectomy who later develop recurrences of this

disease, accessory spleens are responsible for such recurrence in a small group (1 or possibly 2 of our 6 cases). In the majority of cases, accessory spleens are absent or, if present, are not responsible for the disease, which might be assumed in these patients, to be a disorder of the bone marrow, specifically of the megakaryocytes.

Although accessory spleens are probably important in only a minority of recurrences of thrombocytopenic purpura, a search for them should, nevertheless, be made. We believe that x-ray visualization of the reticulo-endothelial system by means of thorotrast will prove a useful and safe procedure. The oft quoted dangers (3) of thorotrast should, we feel, be no deterrent to its use in



FIG. 4

cases like these, where therapy other than accessory splenectomy has so little to offer.

The remaining six cases of our series (table II, Cases 9-14) comprise a group whose course was essentially unaffected by splenectomy. Of these patients, three were x-rayed after Thorotrast, one was explored abdominally for an accessory spleen and two came to post-mortem examinations. In only one patient was an accessory spleen found.

*Case 14. (H. S.)* A housewife aged 29 years was first admitted to The Mount Sinai Hospital on October 23, 1943 with a history of joint pains for three years and increased vaginal

bleeding for one year. In addition, for the past year, numerous purpuric spots appeared on her skin associated with epistaxis and bleeding gums. The blood findings showed a hemoglobin of 40 per cent, red blood cells, 2,580,000; white blood cells, 7,100; platelets, less than 5,000. Bone marrow aspiration revealed a cellular marrow with an increase in the nucleated red cells and megakaryocytes showing little or no platelet formation. Operation was performed on January 11, 1944. A spleen slightly larger than normal with two accessory spleens was removed. Following splenectomy, platelets rose to 130,000 but before discharge had returned to the pre-operative level. She continued to bleed and received five transfusions following which there was some improvement. She was discharged to the out-patient department, where she reported occasional mild nose bleeds. After a few years she became pregnant, had an uneventful delivery and was apparently well. One year before her last admission, she began to have prolonged menstrual bleeding, nose bleeds and petechiae. She became progressively worse and was re-admitted to the semi-private pavilion under the care of Dr. A. Richman.<sup>3</sup>

11/24/49 The blood examination at this time revealed:

Hemoglobin .....	27 per cent
Red blood cells.....	2,850,000
White blood cells .....	20,500
Platelets.....	10,000
Reticulocytes .....	12 per cent
Nonsegmented neutrophils.....	7 per cent
Segmented neutrophils .....	65 per cent
Eosinophils .....	0 per cent
Lymphocytes .....	24 per cent
Monocytes .....	4 per cent
Normoblasts.....	12/100 white blood cells
Pinch test .....	positive
Tourniquet test .....	positive
Coagulation time .....	10 minutes
Clot retraction .....	none in 24 hours

*Bone Marrow Aspiration*

Total nucleated count:.....	75,000 per cubic millimeter
Megakaryocytes:.....	44 per cubic millimeter

*Differential*

Myeloblasts .....	1.2 per cent
Myelocytes .....	10.4 per cent
Eosinophilic myelocytes .....	0.4 per cent
Nonsegmented neutrophils .....	19.2 per cent
Segmented neutrophils .....	8.0 per cent
Eosinophils .....	1.6 per cent
Lymphocytes .....	2.0 per cent
Hematogones .....	0.4 per cent
Proerythroblasts .....	0.4 per cent
Erythroblasts .....	7.0 per cent
Normoblasts .....	49.4 per cent

The blood and marrow findings were almost identical with those found at the time of her first admission. The bleeding was prolonged and un-remitting. Thorotrast was considered for visualization of accessory spleens but an exploratory operation was deemed more advisable. After several transfusions a laparotomy was performed by Dr. L. Colp and a cherry-sized mass of tissue was removed. Pathological examination showed this to be hyperemic lymph nodes without significant change. She continued to bleed intermittently and received

<sup>3</sup> We are indebted to Dr. A. Richman for permission to publish these findings.

numerous transfusions. The platelets rose to 60,000 but returned to the pre-operative level in a few weeks. She was sent home for a short time but was readmitted because of profuse bleeding. In view of the fact that most of the bleeding was vaginal, sterilization by radiotherapy was started. She continued to receive transfusions and radio-therapy, but developed a cerebral hemorrhage. At first there was slight weakness of the right side, but after several days the paralysis became marked. She had Jacksonian convulsions, lapsed into coma and died.

*Autopsy findings* were those of purpura hemorrhagica, with petechial hemorrhages in skin and all viscera, considerable gastro-intestinal hemorrhage without ulceration, large ecchymoses in both renal pelvis, and a large cerebral hemorrhage. There was bilateral bronchopneumonia involving chiefly the lower lobes. On the under surface of the left diaphragm, 4 cm. above the tail of the pancreas, there was a 4.0 x 2.5 x 1.0 cm. accessory spleen. This showed no significant abnormalities on microscopic section.

*Comment:* The disease in this patient lasted eight years. A bleeding tendency mild or severe, was present throughout this period except for a single prolonged remission associated with pregnancy. Splenectomy, performed one year after onset, seemed not to affect the disease except for a transient clinical remission associated with a rise in platelet count to sub-normal levels. Late in her course, a search was made for an accessory spleen by means of exploratory laparotomy. This was unsuccessful but post-operatively she has had a remission exactly similar to the one following her splenectomy. Death finally ensued, as the result of a cerebral hemorrhage. At post-mortem examination a small accessory spleen was found.

What, then, was the significance of the accessory spleen in this case? This, of course, must be a matter for conjecture, since no direct evidence on the point can be obtained. Considering the lack of effect produced by the original splenectomy with removal of accessory spleens, it seems unlikely that removal during life of the small accessory spleen found at autopsy would have proved beneficial.

In the other five patients comprising this second group (table II) no other accessory spleens have been demonstrated. These patients were all unaided by splenectomy. It seems, therefore, that this is a type of thrombocytopenic purpura unrelated to "hypersplenism"; that in these cases there is lack of platelet formation due to some factor as yet undetermined.

#### DISCUSSION

Although there is a high proportion of accessory spleens found at post-mortem, their presence does not necessarily implicate them as responsible for the deaths reported in purpura hemorrhagica (Case 14). Clinical improvement in a patient and return of platelets to normal levels for one year or longer following removal of accessory spleens would seem to be good evidence that these spleens were responsible for the recurrence. A study of the literature on accessory spleens in recurrent purpura reveals an unconvincing body of evidence (4,5).

Finkelstein (6), in 1921, was the first to call attention to the problem, but he presented no case reports. A paper quoted by most authors is that of Morrison *et al* (7), who report a patient in whom an accessory spleen was not removed at the time of the splenectomy. Following operation there was recurrence of bleed-



ing, and a prolonged bleeding time although the platelet count was recorded as 320,000 per c.mm. The patient was followed for a number of years during which time she underwent an appendectomy without disturbing the accessory spleen. Subsequently she became pregnant, had an uneventful delivery, and has not been seen since that time (8).

In a recent review by Thorek *et al* (9), the authors state that the incidence of recurrent primary thrombocytopenia closely parallels that of accessory splenic tissue. In the single case report they were unable to prove such a relationship in their patient. A 22 year old woman had recurrence of purpura following splenectomy. One month following removal of accessory spleens, bleeding recurred and the platelets were low. On re-exploration no additional splenic tissue could be found.

On the other hand, the reports of Doan (10), Evans (11) and one of our own case reports would definitely implicate the accessory spleen as responsible for the recurrence of purpura.

#### SUMMARY AND CONCLUSIONS

1. A complete clinical and hematological remission several months or years post-splenectomy followed by recurrence of purpura should make one suspicious of an accessory spleen or spleens as responsible for the relapse.

2. Visualization by means of thorotrast is a helpful method to determine the presence and locations of such accessory spleens.

3. In the majority of patients in our experience, accessory spleens were not responsible for the recurrence of purpura following splenectomy.

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## A SURVEY OF SOME RECENTLY PROPOSED CHEMICAL TESTS FOR MALIGNANCY\*

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Cancer research, and more so, cancer diagnosis are subjects wrought with tantalizing difficulties. The subject has been glamorized for an impatient public, and is thus beset with emotions. Therefore I shall attempt to review the field with caution and criticism, perhaps benefiting from the absence of personal involvement—*sine ira et studio*.

The motives of the individual scientist in his investigations are many: the urge to unravel fundamental laws, the utilization of scientific observations for practical humanitarian, or anti-humanitarian purposes, personal ambition, or pure intellectual curiosity. The methods used may be inductive or deductive, they may be experimental or observational. But regardless of motive and approach the results of scientific activity fall, as I see it, into two categories: Discovery and Invention.

Discovery of truth means the finding of a unique answer to a question (1). While the discoverer must be conditioned by time and place, or to put it differently, while some discoveries are sometimes "in the air" and ripe to be made, discovery requires the spark of genius which can neither be forced nor ordered, neither be organized nor bought.

Invention offers many solutions for whatever problem has been posed. The simplicity and elegance of the invention reflects the ingenuity of the inventor. The number and practicability of the solutions bears a relation to the intensity of effort, to the number of researchers employed, to the material means that are available. Thus, the progress of invention, which is often synonymous with technological progress, is subject to great variations with epoch and country—but the occurrence of discovery parallels the occurrence of genius which one would picture as evenly, but thinly spread through time and space. One might emphasize the difference in the psychological situation; the feeling by the discoverer of accomplishment—the continuous striving for higher perfection by the inventor.

The problem, or the multiplicity of problems, which constitute the cancer problem are awaiting a solution, perhaps a complicated solution, but a unique solution. There is some truth still hidden which awaits discovery. The problem of cancer diagnosis and therapy, cure and prevention fall into the domain of invention. Evidently, and as the history of antiseptics, of vaccination and of chemotherapy during the last 100 years has demonstrated, knowledge of the cause is vital for finding the cure of disease. That does not mean that we should put our hands in our laps to wait for the discovery of the cause of cancer, but one must be aware that the search for a cancer test, in our present state of

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knowledge, may very well lead—if anywhere at all—rather to a better understanding of malignant processes than to a practical diagnostic procedure.

We live in an age of intensive invention, particularly in the field of chemistry. One has synthesized, that means invented, thousands of carcinogenic compounds, one has invented numerous processes for the isolation of vitamins, antibiotics and hormones, after the existence of the individual compounds had been discovered. But one should beware of the hope that the apparatus of invention, the multiplicity and extensiveness of effort, can by itself force Nature to reveal what seems to be one of its rather fundamental principles. If the causes of malignant growth were already discovered, one might set out to invent methods to recognize the presence of such processes, but at present such a method would have to be discovered in a poorly charted territory.

Let us consider the practical side of a test for malignancy, and what are its requirements and purposes.

1. To recognize the presence of malignant growth in order to undertake therapeutic measures. Thus, not only the presence, but also the site of the tumor must be found.

2. To differentiate between malignant and non-malignant tumors and obstructions, once pathological symptoms in a given location or circumscribed area of the body have been clinically established.

3. To check the success of surgical or radiotherapeutical removal of a recognized malignant neoplasm.

I doubt whether any method could satisfy these three purposes equally well. When talking of chemical tests, one has in mind significant, chemically defined changes in the composition of a body fluid, usually the blood serum, or of an excretion, most often the urine. Or one wishes to consider the changes in the fate of an extraneous substance, e.g. a dye after introduction into the organism. A short survey of the analytical items which form the subject of present-day Clinical Chemistry will illustrate these points.

The chemical and serological analysis of blood serum, plasma, urine, feces, saliva, bile, exudates, transudates and other body fluids and excretions is designed to give us a significant cross-section of the metabolic processes. Evidently, metabolic processes in general take place in the cells and tissues, while the body fluids are primarily concerned with the transport of metabolites and catalysts from one organ to another, the excretory fluids with the expulsion of useless or noxious substances from the body. Hence, the level of concentration of a given compound in the plasma gives us no information on the quantity of this compound in the body, just as counting the passengers on the busses passing Mount Sinai Hospital on Fifth Avenue, gives us no information as to the size and geographic distribution of the population of the city. The chemical composition of the various tissues and organs themselves can only be learned by direct analysis, e.g. of biopsy material.

The chemical analysis of body fluids teaches us signs of metabolic processes, normal and abnormal ones. We find, e.g. in serum,

1. Such normal metabolites as the anabolites: oxygen and all food constituents

such as glucose, ethanol, fat or fatty acids, phosphatides, cholesterol, etc.; the intermediate compounds: amino acids, glucosamine, various phosphoryl compounds, lactic acid etc.; the catabolites:  $\text{CO}_2$ , uric acid, urea, creatinine, urobilin etc.; and a number of inorganic ions: Na, K, Ca, Mg, Cl,  $\text{PO}_4$ . We have learned to deduce from deviations in their concentration the existence of metabolic disturbances.

2. Such disturbances may lead further to the appearance of compounds, not found in the body fluids in health, such as acetone and aceto-acetic acid, creatine, pentose, phenylpyruvate, extracellular hemoglobin, or serum constituents in the urine or urinary constituents in the serum, and special amino acids due to the breakdown of organ proteins.

3. Some normal constituents like cholesterol esters may disappear altogether from the circulation under pathological conditions.

4. Products of microbial metabolism like toxins and antigens and the anti-toxins, elicited by them in the body, are revealed by serological tests which thus detect the presence of microorganisms.

5. Poisons and other undesirable intruders are detected by analysis of body fluids.

6. Finally, drugs and test substances for various body functions are determined in body fluids to guide the physician in therapeutic measures, to test detoxification mechanisms and physiological functions such as circulation time and renal clearance.

Which of these categories of normal and abnormal body fluid constituents could contribute to the detection of malignant tissue in the body?

Some of the most promising approaches to cancer diagnosis are related to this last group of tests. The introduction into the patient's body of radio-active tracer-material has been applied to some more or less specific situations such as radio-active iodine in the diagnosis of thyroid cancer (2). Radio-active diiodo-fluorescein has been found to have a special affinity to tumor tissue and has been employed in the localization of brain tumors (3). Progress has also been made with radio-active phosphorus in work on superficial or otherwise easily accessible tumors (4).

In general the metabolism of the malignant cell resembles that of the organ from which the tumor is derived except for the qualification that aerobic processes are suppressed in the cancer cell. Thus malignant tissue does not contribute any specific pathognomonic substances to the body fluids.

There will be some rather unique situations as for instance in tumors of the endocrine tissue of the pancreas where an inordinate amount of insulin will be detectable in the blood; but this would constitute organ-specificity rather than a specific reaction for malignancy.

The "Defensive Enzyme" theory of Abderhalden was based on the concept that the introduction of certain substrates such as saccharose, starch, protein into experimental animals stimulates the production of corresponding enzymes for instance saccharase, amylase and specific proteinases. The enzyme, specific for placental protein, was used by Abderhalden as a pregnancy test. The same



concept was also applied to tumor protein. A voluminous experimental literature emerged on this subject, but it has not stood the test of time (5).

Nor has the immunological approach to the problem led to any substantial success. Much work has been done from either one of two viewpoints, (a) the production of anti-tumor sera, (b) the detection of specific tumor antigens. This subject is linked to the problem of organ specificity; here, the statement may suffice that tumors do not produce those immunological responses which are the basis of immunodiagnosis and immunotherapy in the case of pathogenic microbial invaders nor do the breakdown products of necrotizing tumors show specificity.

Freund and Kaminer (6) postulated the presence in healthy subjects of specific fatty acids as products of normal fat metabolism, acids which prevent malignant growth. On the other hand, these acids were supposed to be supplanted by different fatty acids in cancerous subjects—acids which protected the cancer cell against the defense of the body and thus promoted malignant growth. This theory of cancer-specific metabolites has not been verified. The experimental conditions of Freund have been too difficult to reproduce, so that no explanation has ever been proposed for Freund's undoubtedly careful observations.

Outhouse (7) has found about 1936 in cancer tissue aminoethyl phosphate, obviously a breakdown product of phosphatides. I am not aware of any sequels to his work or of any diagnostic application.

Observations on occupational malignant disease in chimney-sweeps, workers in the aniline dye and coal-tar industry led to the recognition of the carcinogenic nature of certain coal-tar products, esp. aromatic amines and polycyclic hydrocarbons, a concept which was confirmed experimentally about 40 years ago. Yet, there was no plausible connection between these "tar-tumors" and the spontaneous tumors in man. It was only after the establishment of the Rosenheim-King formula for the steroids, that a connection could be discerned between such generally occurring biological compounds as cholesterol, bile acids, vitamin D and various hormones on the one hand, and polycyclic hydrocarbons with carcinogenic properties on the other hand. Much has been speculated about the analogy of the stimulating effect of the steroid sex hormones on specific tissues and the stimulating effect of carcinogenic compounds as regards the patterns of cell proliferation and, by implication, the underlying cytochemical mechanism (8). Moreover, the transition of steroid compounds by certain chemical reactions, especially aromatization, into carcinogenic hydrocarbons was suspected to be involved in the etiology of cancer. The time might soon come when the validity of this hypothesis of carcinogenesis, which has rather lost favor in recent years, may undergo a definitive evaluation.

What interests us today is the possible usefulness of such ideas for cancer diagnosis. About 12 years ago, Drs. Bloch, Rosenbloom and I (9) carefully extracted 3000 liters of urine of cancer patients. On the basis of recovery experiments with minute quantities of carcinogenic hydrocarbons, we were able to exclude the presence of such carcinogens in cancer urine (10, 11). Incidentally, we found elevated amounts of cholesterol in these urine extracts, but a subse-

quent study of individual cancer urines convinced us, that cholesterolemia is not a diagnostic sign of malignancy, but must be ascribed in individual cases to secondary pathological processes, involving the kidney.

A few years ago, Kögl (12) suggested that the enantiomers, the mirror images of the naturally occurring so-called L-amino acids, be typical constituents of tumor tissue. This brilliant hypothesis was unfortunately not confirmed, thus we may disregard its diagnostic implications.

As stated above, no specific chemical substances, including immunochemical entities, have to date been discovered which are pathognomonic for malignant tissue. Such a discovery would of course not only furnish an unequivocal test for malignancy, but would be of the utmost significance for cancer research in general. Lacking such specific and unique indicator for malignancy—in the terms of analytical chemistry: a qualitative test—one has looked around for quantitative changes in the composition of the body fluids which could indicate the presence of malignant growth. If the chemism of the malignant cell differs from that of the normal tissue cell, as seems reasonable to assume, may we expect to find such a difference reflected in the composition of serum or urine? The various serum constituents, for which I have given examples, have been studied in millions of sera from patients with known diagnoses, malignant or otherwise, and any correlation of their level in the serum with neoplastic disease would have become known long ago.

Certainly 99% by weight of the serum solids are known to us. There must be yet numerous important substances, e.g. hormones, vitamins and enzymes which are most potent biologically, but which constitute less than 1% of the solid matter in serum. These compounds, amongst which there may well be one or several undiscovered "cancer indicators", could be free or bound to the protein of the serum.

We have not yet discussed the plasma proteins. They constitute ca. 5/6 of the serum solids, but the chemistry of protein is replete with a great many unanswered questions. Thus, the knowledge of the clinical significance of plasma constituents is limited in this important item. The plasma proteins are said to comprise albumin, globulin, and fibrinogen; only the latter is regarded as a chemically uniform protein.

Globulin consists of a great variety of subfractions. The older methods of fractionation by salting out with sodium sulfate or ammonium sulfate have been superseded by methods combining precipitation by salts, alcohols and cold temperature. Edwin J. Cohn (13) and his school have described numerous fractions. Amongst these one finds globulins associated with lipoids, with carbohydrates, and globulins with antibody or antitoxin properties.

Less is known about the subfractions of serum albumin. These fractions, globulin and albumin and their subfractions are defined by their solubility in water and electrolyte (salt) solutions, by their sedimentation rate, and at least half a dozen of the main fractions by their mobility in the electric field, i.e. by electrophoresis. Their physico-chemical properties are the basis for their classification and separation from each other.

In some rare instances, pathological protein fractions with physico-chemical

properties of their own are found besides the normal fractions in some disease and are almost pathognomonic (14). No such specific anomalous protein fractions have been observed in cases with malignant tumors.

Frequently deviations from the usual proportions of the normal fractions may be anticipated in disturbances of physico-chemical equilibria in the body. The loss of albumin in nephrosis and related renal conditions produces inversion of the albumin/globulin ratio with a decrease of total protein. The rapid accumulation of antibodies of globulin character in certain infectious diseases likewise reverses the albumin/globulin ratio, but here with an increase of total protein. In all these cases we are dealing with shifts in the quantity of some protein fractions characterized by physico-chemical properties.

The modern progress of protein fractionation has neglected the question of chemical composition of these fractions. Older analyses exist for the constituent amino acids of albumin and of globulin, but they are much less accurate than the data known for such crystalline protein individuals as pepsin or insulin. A detailed analysis of a globulin subfraction, obtained by salting out or electrophoresis, would be of statistical interest only and would not be reproducible because such a protein subfraction comprises numerous individual proteins, including, e.g. antibodies against a variety of diseases to which the subject has become immune, which are of similar molecular weight, shape and electric charge, yet may differ widely in their chemical composition.

In collaboration with Tuchman and Reiner we have shown that the sulfur content (indicative of cystine plus methionine) and the so-called tyrosine reaction (indicative for tyrosine and also for tryptophan) of the albumin and the total globulin undergo considerable variation (15, 16, 17, 18). For normal individuals, either man or other species, the individual deviations from average values are small enough to permit the use of these averages for analytical purposes. But whenever the albumin/globulin ratio is disturbed, significant changes occur in the chemical composition of the fractions.

As early as 1887, Halliburton described the fractionation of serum albumin by heat coagulation. The urinary albumin is another case in point; it differs from the serum albumin of the same individual according to Grabfield and Prescott (19) who were concerned with the urinary albumin in Bright's disease. They noticed that the ratio N/S in urinary albumin or protein is substantially higher than in serum albumin. This quotient is a measure for the amount of sulfur-containing amino acids, i.e. cystine and methionine. The ratio in serum is about 16% N to 1.4% sulfur. In urinary protein the nitrogen percentage is the same, but the sulfur percentage drops so that the N/S ratio increases; in some instances no sulfur is present, giving a ratio "infinity". Such a sulfur free albumin may either be a catabolic product of serum albumin or it may be due to selective preferential excretion of a sulfur-free fraction pre-existing in the serum albumin.

The application of improved methods of amino acid analysis to more detailed fractions of plasma proteins may bring to light hidden disease-specific differences. This concept and approach will gain value, when the specific chemism of the

neoplastic cell, its amino acid constellation and its enzymatic physiognomy will be better known.

As stated previously, chemical cancer research has not favored these lines of thought, and thus a systematic approach has been lacking. Nevertheless, it appears plausible to fish, as it were, in the protein pool for cancer-specific features, without definitive knowledge of what one should expect to find. It is this empirical approach to a serum reaction for malignancy which has been instinctively taken by a number of investigators in recent years. There seems little doubt that such important tests as the Wassermann Reaction, which was likewise not understood at the time of its discovery, have inspired and stimulated such attempts.

Observations in this direction date back half a century. Petry (20) observed in 1899 a diminution of the heat coagulability of tumor protein. In 1925, H. Kahn (21) observed the diminution or complete absence of the so-called albumin A fraction in sera of cancer patients, but pointed out cautiously, that a similar defect occurs in hepatic and renal disease and infectious states. Similar shifts within the albumin sector underly changes in the nephelometric behavior of serum when precipitated with certain concentrations of ammonium sulfate, but again the phenomenon is not cancer-specific, but occurs also in tuberculosis (22).

In 1936 G. Jerzy Glass, then in Warsaw, reinvestigated sundry observations recorded in the literature on the heat coagulation of serum (23). It is hardly necessary to mention that any reaction of this type requires strictly reproducible and well defined conditions of temperature, time, shape of reaction vessel and also a clear definition as to what is meant by coagulation. The first visible symptom on heating serum is the appearance of turbidity, subsequently gelation sets in, which in its early stages is reversible by shaking—we talk then of a thixotropic gel; the final stage only should be referred to as coagulation, when the test tube with coagulum may be inverted to show complete—and irreversible—solidification. Glass distinguishes three degrees of elevation from the normal level of the coagulation point; he uses complete coagulation as his criterion. The first degree is an elevation from the normal level of 75–80°C. to the range 81–84°C. The second degree comprises coagulation points from 85–100°C., the third degree is reserved for sera which do not coagulate at 100°C. There exists a certain correlation between protein content and coagulation temperature; sera which do not coagulate at temperatures up to 92°C., will not coagulate at all; sera not coagulating at or below 100°C. never contain more than 7% protein.

The phenomenon is definitely an “albumin” phenomenon; globulin is not essential for serum coagulation. The complicated enzymatic apparatus responsible for the formation of fibrin from fibrinogen does not come into play, since the reaction is carried out on serum, not on plasma. This eliminates the complications which must result from the supraposition of enzymatic and thermic coagulation of fibrinogen upon the purely thermic coagulation of the albumins. Glass soon recognized (a) that the minor elevations of coagulation points of the first degree had little if any significance, (b) that coagulation defects occurred



to a high percentage in certain malignancies, namely of viscera, bones, also of thyroids and prostate, but were not frequent in malignancies of skin, mouth, lung, breast and female genitalia. He also observed a high incidence of the albumin coagulation defect in the following groups of non-neoplastic diseases: complications of pregnancy, nephrosis, extensive tissue destruction by burns or frostbite, infective disease such as typhoid, pyogenic infections, pneumonia, and especially arthritis and pulmonary tuberculosis.

The defect was absent or rare in non-pyogenic inflammatory disease, most hepatic conditions, fractures, diabetes, peptic ulcer etc. It may be worth while pointing out, that in liver affections the serum globulins rather than the albumins are out of kelter, as demonstrated by the positive findings in liver diseases of "globulin lability" with such tests as Takata-Ara, cephalin flocculation, formol gelation, thymol turbidity and other converging globulin lability tests. While this test of the albumin coagulation defect has therefore not been proposed as a test for malignancy, it may be of value for certain differential diagnoses if properly understood. Elevations will for instance occur in cases of ascites of renal, cardiac or neoplastic origin, but not in those of hepatic origin. Glass reached the conclusion, with which we fully agree, that the albumin coagulation defect is not specific for one disease entity, but is a test for severity of disease.

This view is, e.g. expressed by the authors of a recent reexamination of the iodoacetate thermal coagulation test (24).

"The distribution of the indexes in these groups was such that it was not possible to choose a range of iodoacetate indexes that was sufficiently inclusive of the values in healthy individuals and sufficiently exclusive of those patients with cancer to form the basis of a useful diagnostic test". . . . "the qualitative defect in the serum proteins, which is revealed by the thermal coagulation tests, is not specific for cancer, but is merely one manifestation of the reaction of the organism to noxious stimuli."

This reference is made specifically to a test which has recently been proposed and which is based upon a similar correlation of chemical findings with diagnoses. The test consists in the coagulation of serum at 100°C. in the presence of iodoacetate under a given set of experimental conditions. The results are described by an arbitrary "iodoacetate index" which is proportional to the minimum ratio of iodoacetate to protein necessary to prevent coagulation. This proportion is less in most cancer sera. The test has gained wide publicity. According to the consensus of responsible investigators its false positives and false negatives—false from the view point of cancer diagnosis—show a similar distribution amongst the various sites of tumors and amongst the various severe non-neoplastic diseases as the albumin coagulation defect investigated by Glass. Some purveyors of sodium iodoacetate have exploited the use of this, otherwise commercially uninteresting chemical, so that Huggins(25) who has proposed this test felt compelled to write:

"... A recent advertisement of the American Reagents Company concerning a set of reagents for determining the iodoacetate index of serum contains a statement which is not true, namely, that a positive reaction indicates cancer. Last year it was found in our laboratories that halogenated acetates, of which the most powerful is sodium iodoacetate, had

the property of preventing serum albumin from forming a coagulum on heating. It was also shown (Huggins, C., Miller, G. M., and Jensen, E. V.: *Cancer Research*, 9, 177, 1949) that smaller quantities of this inhibitor are required to prevent coagulation of the serums of most patients with cancer than are needed for a similar effect with normal serum. It was emphasized at that time that the defect is not specific for cancer since it also occurred in certain inflammatory conditions. Further experience has confirmed these statements. I should like once again to draw the attention to the fact that a low iodoacetate index of serum is not diagnostic of cancer but for clinical purposes must be interpreted in the light of all other clinical and laboratory data available, to which, however, it is supplementary. While I have had no contacts with the American Reagents Company, nor have I used their "set" of reagents, I know that determination of the iodoacetate index requires a painstaking quantitative chemical technic, and I doubt that it can be done successfully under less rigorous conditions."

A less charitable comment by another group who have reexamined this test reads in part (27):

"... The method originally described is not reproducible and is useless because its endpoint is uncertain.

The recent modification of the method proposed by Huggins' group is more reproducible, but also more insensitive. . . . The rate of failure will be considerably higher in early cancer.

. . . Its promotion as a diagnostic tool is to be deplored. In its present form, this procedure is useless and confusing as a diagnostic test for cancer."

Another test which has recently gained much attention is the Heat Coagulation test, or as it has more properly been renamed, the Heat Precipitation test of Black, Kleiner and their coworkers (28). This test follows in some way the opposite pattern than the albumin coagulation defects previously surveyed. As it deals with plasma, the fibrinogen is present when the tube with the plasma, five-fold diluted, is immersed under certain standard conditions into a boiling water bath for 10 seconds. The increase in turbidity is determined objectively by a photoelectric colorimeter. Apparently the ratio of albumin to fibrinogen and the protective action of the former for the latter interact in such a manner, that a greater degree of turbidity is produced in a majority of malignant sera, but according to the authors themselves also in the case of "some pregnant women and some—but not all—patients with pulmonary tuberculosis, acute rheumatic fever or quantitative disturbance of the blood proteins" (the latter refers to nephrosis and other edematous states). The authors, in their last publication (29) state, that "the reaction is certainly not specific since ailments other than malignant disease can and sometimes do cause abnormal reactions". An inspection of the statistical material makes it fairly clear that the false positives and false negatives run in general parallel to those of the albumin coagulation defect tests, in other words, enhanced heat precipitation of plasma is a "defect" correlated with elevated heat coagulation point of serum and with a low iodoacetate index for prevention of coagulation.

All these phenomena are, as stated previously, expressions of changes in the serum albumin; one may call these changes qualitative, if one considers the amino acid composition and perhaps the geometric configuration of the total albumin, or quantitative, if one presumes that the albumin sector, like the

globulin sector consists of a number of species, similar in their physico-chemical behavior—they all correspond to the definition of albumin—but differing from each other by amino acid constitution, and molecular configuration and architecture.

Similar considerations have been adduced by Black and Kleiner for a second test (30). According to prior observations by Savignac a high percentage of cancer plasma samples is distinguished from normal plasma by the following property. When heated with a certain amount of methylene blue under standard conditions, the decoloration, i.e. the reduction of the dye is slower in the pathological than in the normal specimens. This difference is ascribed to the smaller amount and/or smaller accessibility of cysteine sulfhydryl groups in the malignant plasma. But here, again the percentages of false positives and false negatives are much too high for a diagnostic test. In an excellent survey which discusses the evaluation of more than sixty diagnostic tests for cancer, Homburger (31) reports a preliminary evaluation of this test by Benotti who found in a limited series only eleven positive tests amongst 29 cases of proved cancer and 29 negatives amongst 38 non-cancerous subjects. Thus, one remains unconvinced of the usefulness of these measures for diagnostic purposes and would rather see them elaborated and developed into the direction of a rational explanation; this might contribute much more to the core of the cancer problem than an empirical test of admittedly inadequate scope.

A novel approach to the interrelation of the serum proteins in health and disease has recently been made by Harkness (32) in England. This author starts from the assumption that albumin, globulin and fibrinogen which he treats as individual entities, are in plasma in an equilibrium with each other and with some molecular complex embracing all three species. On this hypothetical basis he derives an equilibrium constant  $K$ . For the simpler system albumin-globulin in serum, under the assumption of an A/G ratio of 1.5, the majority of the  $K$ -values fall on the line  $K = 0.5090$ . All deviations are situated below this line and Harkness observed their correlation with pathological states. He then devised a formula for  $K$  in plasma, based on a composition of 59 parts albumin, 41 parts globulin and 6.8 parts fibrinogen. In this system all deviations are again on one side of the straight line for  $K$ , which for the plasma equilibrium assumes a maximum value of 0.3947. If the A/G ratio is plotted as abscissa and the A/F ratio as ordinate, the  $K$ -values may be assembled in closed curves (fig. 1). It is in the nature of this graphic presentation that the vortex with the maximal  $K$ -value is situated at the intersection of  $A/G = 1.44$  and  $A/F = 8.67$ , the values considered as normal and as basis for  $K$ . Harkness then goes on to prove that the plasma data of normal subjects fall into the right upper quadrant of the diagram. In the case of any illness, that affects the plasma protein picture, the  $K$  point usually moves along the "orthogonals" which indicate the shortest path for a maximal change in  $K$  with a minimum shift in protein composition. In severe disease, the values move into the left lower quadrant; once the  $K$ -value has dropped in this region below 0.380, it represents irreparable damage to the body and a fatal outcome is certain. On the other

hand, in the course of recovery, the K-point traces its path backwards into the right upper quadrant. Having clarified the non-cancer-specific nature of the test, the author suggests individual situations where a movement of K to the left and downwards would favor a diagnosis of malignancy and a K moving to the right and upwards would be strongly against such a diagnosis.

It would seem to the physico-chemist that the constant K and the underlying assumption of an equilibrium between the three plasma proteins are purely hypothetical and fictitious. But a look at the figure shows that one deals actually with a graph of  $A/G$  vs.  $A/F$  and that the K curves are nothing but a

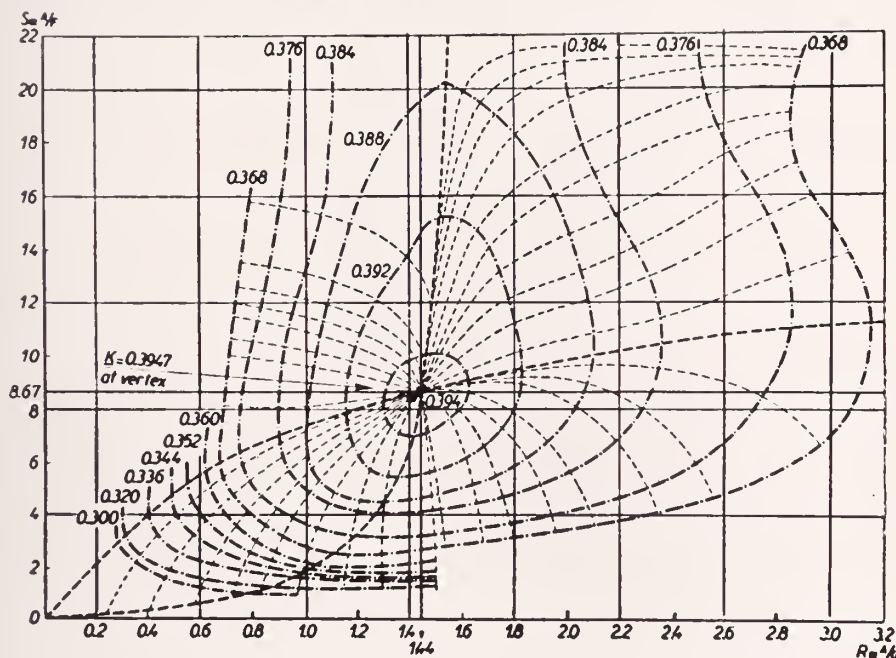


FIG. 1. Nomogram for estimation of K from  $R = A/G$  and  $S = A/F$ . Contours of equal K values. Orthogonals of maximum change in K with least change in protein fractions (From Harkness, 32).

handy device to define certain regions on that graph. This does not detract from the value of the data, which are simply based on chemical separation and Kjeldahl determinations. If one correlates them with the albumin coagulation defect and the plasma heat precipitation effect, one might anticipate that these effects be predictable by the combination of  $A/G$  and  $A/F$  ratio. This could be tested: if there is a good correlation it would justify the assumption that albumin and globulin may be treated as entities of constant properties within the scope of this test; otherwise the alternative assumption would be in order, that the tests mentioned can tell us—beyond the purely mathematical proportion—something about qualitative changes of the protein fractions.

Whatever the unexplored rationale of all these tests may be, they are not suitable as yes-or-no tests to answer the question "Has this patient malignant



disease or not?" It has been said that they may serve for orientation and screening. Both the wisdom and the need of such an application are questionable. In any event, it seems undesirable indeed to put a tool of this nature into the hands of the physicians, a great many of whom rely for their diagnoses on laboratory tests, interpreted for them by the laboratory men; it seems even worse to keep the public and the patient in the belief that such a yes-or-no test exists when in fact it does not.

Should the conscientious chemist carry out such a test and report its outcome with the corollary or qualification, that it does not necessarily mean a diagnosis of cancer or of not-cancer respectively? What is the physician to reply to the patient who unfortunately reads about it in the daily paper and demands the test? One can not compare this situation with, for instance, a screening of some military or civilian population for syphilis, however inadequately the serological technique might often be performed; because syphilis is no more the dread incurable disease it used to be. Clinical chemists and pathologists throughout the country feel that the premature announcement of insufficiently evaluated tests, their inflated representation in the press and their exploitation by irresponsible laboratories is against the best interest of the public. It seems rather surprising that one should find listed as "among the year's more spectacular developments . . . new evidence relating to changes in blood serum of cancer patients opening up the possible development of a practical blood test for cancer", while private laboratories send out cards announcing "a new department for serodiagnosis of cancer" or "that the . . . test in cases of suspected malignancy is carried out in this laboratory". The originators of such tests have the moral responsibility to confine their use as an adjunct to the established clinical methods of cancer diagnosis.

So much for these tests based on what one should designate as non-cancer—specific albumin defect tests or tests for severity of disease. There are other aspects which should be briefly mentioned. No reference will be made to the cortical hormones; they do so many things and so many things are done to them, that one should wait until the fog rises to see whether they have any direct bearing on cancer and cancer diagnosis.

We have surveyed and scrutinized all blood constituents for their possible usefulness in cancer diagnosis, but have not yet spoken of the enzymes. As repeatedly stated, no specific compounds have been found in tumor tissue that did not occur in normal organs. There are of course quantitative shifts, e.g. the nuclear proteins are known to be increased in cancer tissue at the expense of the cytoplasmic proteins. The same absence of cancer specificity holds for the enzymes. As J. Greenstein says (33):

"Each normal tissue is characterized by the presence of an individual pattern of enzymatic activity which may serve to distinguish it from all other tissues. Tumors have qualitatively the same enzymes as normal tissues."

Blood serum, generally speaking, is not a carrier of enzymes and under normal conditions its content of some scattered enzyme molecules is negligible in

comparison to that of cells and of the digestive juices. The blood serum and the lymph serve the transport of the nutrilites (proteins, lipoids and carbohydrates), whereas the transport of enzymes within the body is usually carried out by the white blood corpuscles, an arrangement which keeps the enzymes separate from their substrates during transport. There are however situations when enzymes appear in significant amounts in the serum, e.g. as the result of pathological processes in glandular organs, leading to obstruction and regurgitation.

Transfer of an enzyme from one organ to another may occur under a variety of natural experimental conditions. Virtanen (34) demonstrated that feeding of pancreatic lipase leads to an increase of esterase in the liver, presumably by a recombination of the prosthetic group, common to both enzymes. In pulmonary tuberculosis (35) it is a defense mechanism of the body which mobilizes and commandeers the available esterases from the visceral organs to the lungs for an albeit futile attack on the lipid-covered invader. This concept of enzyme migration in response to pathological stimuli, about which I have often speculated, has recently been beautifully exemplified by Otto Warburg (36).

The glycolysis of glucose to lactic acid, the typical reaction of tumor tissue even under aerobic conditions, is brought about by the successive action of 11 enzymes, 8 of which have been isolated in pure crystalline form. Warburg felt that this progress in enzyme chemistry justified a reexamination of the tumor problem. In a study of the distribution in normal and in tumor rats of zymohexase, the enzyme responsible for scission of hexosediphosphate into two molecules of triosephosphate, he found the overwhelming share of this enzyme in the muscles.

One gram muscle contains about 1.5 mg. of the enzyme, thus ca. 125 mg. in the total musculature of a 200 g. rat. One gram of tumor tissue contains 0.09 mg. of zymohexase, thus for a 20 g. tumor 1.8 mg., which is a little more than 1% of the amount in the musculature. The quantities in the other organs are negligible. The serum of normal rats contained the small but constant amount of 0.3  $\mu$ g, but in tumor rats this serum zymohexase titre was increased up to twenty-fold, depending on the size of the tumor. In separate experiments it was shown that 98% of the enzyme, when injected into the circulation, disappeared in 24 hrs. from the blood stream.

Thus, Warburg concludes that the tumor, incapable of synthesizing fermentation enzymes, draws them from the blood serum, which in turn obtains them from the muscle, by far the richest source of these enzymes. This assumption is supported by experiments with another enzyme, the reducing fermentation enzyme whose active group dihydronicotinamide hydrogenates pyruvic to lactic acid. It was possible to show the identity of this enzyme from muscle and from tumor tissue by the crystal form of its mercury salt, by optical rotation, molecular weight, ultraviolet absorption spectrum and by the strength of its enzymatic activity. We think that this approach, which is based on a tumor-specific enzyme system may lead, amongst other results, to a diagnostic test. Similar considerations might apply to phosphamidase, an enzyme found by

Gomori in especially large amounts in the nervous system, but also in malignant epithelial tumors (37).

Let us finally assume that some test be found which satisfies the highest requirements for accuracy and specificity. It might be based on one of the two following mechanisms: (a) either on the appearance in the serum of a product or byproduct of tumor metabolism, which would thus be subsequent to the development of a tumor. Evidently, its dilution in the circulating blood will lower the sensitivity of the test and it is easy to foresee that a positive test will require substantially more than a few tumor cells such as might be fully convincing for a histological diagnosis. Such a test, based on some expression of metabolism of actual tumor tissue could supply information concerning the success or failure of surgical removal of the tumor.

(b) On the other side, one may conceive of a test indicating some sort of transformation of the metabolism of the organism to a state which would make the development of malignancy possible and likely to occur. Such a test, if it was ever found, used in conjunction with a valid etiology of malignancy would form the ultimate basis of systematic cancer prevention. Such test would also indicate whether the preparedness or trend to tumor formation has been abolished by the therapeutic intervention.

Until the time when such ideal chemical diagnostic tests shall be available, the most important part in the diagnosis of malignancy will be played by the clinician's own keenness of observation and judgment. Once the presence of a tumor has been proved and its location ascertained, the diagnosis of malignancy is up to the morphologist; in certain cases he will be greatly aided in prognosis by the experimental pathologist, using the elegant technique of Harry S. N. Greene of heterologous transplantation.

Meanwhile the search for chemical tests continues. We all join in the hope that urgently needed conventions will be established for the correct clinical evaluation and the competent statistical treatment of diagnostic cancer tests (38), in order to protect the patient against mental anguish and economic loss on one side, and dangerous oversights on the other. What is perhaps even more important, we must have a mechanism to separate the wheat from the chaff and thus be certain that a future satisfactory chemical test for cancer will not suffer from discreditable precedent, but occupy its deserved place.

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## THE USE OF RADIOACTIVE AND STABLE ISOTOPES IN HEMATOLOGY\*

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Within the past few years radioactive and stable isotopes have become available in sufficient quantity for investigation and therapy. In the field of hematology new methods utilizing these isotopes have been developed and applied to various physiological and clinical problems; several of the radioisotopes have been used with some success in the treatment of certain blood dyscrasias.

The use of isotopes as tracers depends upon the fact that they behave in the body exactly as do the same naturally occurring elements; they can be detected by means of a suitable instrument, and amounts small enough may be given so that the normal biochemistry and physiology of the body is not disturbed. There is an important difference between the radioactive and stable isotopes; the radioactive variety are detected by a Geiger-Mueller tube, electroscope or electrometer because they emit particles or rays as a result of nuclear disintegration; stable isotopes are useful as tracers because naturally occurring elements have a uniform isotopic composition and any deviation from the normal state of a specimen may be detected by the mass spectroscope. A compound enriched with a stable isotope or made radioactive by incorporating radioactive atoms into its structure, may then be followed in its metabolic wanderings through the body. The comparatively limited amount of work done with stable isotopes as compared with their radioactive twins is due to the high cost of the stable isotope, a lower order of sensitivity than the radioisotope and the relative difficulty in detection. Stable isotopes have the advantage of being free of radioactivity.

Of the radioactive isotopes available, phosphorus (P-32) has been used extensively both in research and therapy, iron (Fe-55) and (Fe-59) have been used as tracers in hematologic research while gold (Au-198) and sodium (Na-24) have been of some therapeutic value. Of the stable isotopes, only nitrogen (N-15) has thus far yielded information of significance when used as a tracer. In addition, strontium has been used to a limited extent as well as colloids of yttrium and zirconium.

The problem of determining the life span of the human erythrocyte is one which has intrigued physiologists for many years. The methods employed in this investigation in the past have included, among others, a study of the quantitative relationship between hemoglobin production and bile pigment excretion, the survival time of transfused red cells as determined by means of differential agglutination, and the rate of disappearance from the circulation of sulfhemoglobin tagged erythrocytes. These and other studies have yielded widely variable results for the life span of the average red cell, ranging from a few days to almost seven months. A correct solution was finally obtained by employing red cells labelled with nitrogen 15.

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Shemin and Rittenberg demonstrated that glycine labelled with N-15 when fed to animals was incorporated in the protoporphyrin of the red cell (1). The tagged erythrocytes could then be observed in the circulation throughout their life span. Since, following the destruction in the red cells of the body the N-15 was not reutilized in erythropoiesis, a sensitive method became available to determine red cell longevity.

One of the authors ingested N-15 tagged glycine over a three-day period (2). Blood samples were then collected at frequent intervals, the hemin isolated from each specimen and analyzed for N-15 content. The isotopic concentration of the hemin in red cell aliquots increased rapidly during the first three weeks to a maximum, and then fell sharply to a low level. By analysis of the data, the life span of the red cell was estimated at 127 days.

Although radioactive iron may be used to tag red cells, when these cells disintegrate, the liberated iron is reutilized by the marrow in further erythropoiesis. Because of this, it is not possible to determine accurately the length of life of the red blood cells in a normal person. However, Finch *et al.* (3) have demonstrated that in patients where effective reutilization of radioactive iron from broken-down red cells is blocked by excess iron stores or where there is pathologic arrest of bone marrow function, measurements of red cell longevity utilizing radioiron tagged red cells can be made. Their estimate is about 122 days, which agrees closely with the value obtained by the N-15 method.

The present concept of iron metabolism includes important contributions made by a host of investigators utilizing the radioactive isotopes, Fe-55 and Fe-59 (4-10). Following ingestion, iron, organically bound in the food, is hydrolyzed and reduced to the bivalent form by the combined action of the hydrochloric acid of the gastric juice, sulfhydryl groups in the food and probably ascorbic acid. This reduction is important because in the human, iron in the ferrous state is more easily absorbed than the trivalent form. In the absence of hydrochloric acid, if iron is ingested in the inorganic form, it will nevertheless be absorbed. The absorption of iron into the blood stream is regulated by a unique protein, apoferritin, found in the mucosal cells of the upper gastro-intestinal tract. This protein is capable of combining stoichiometrically with 23% of its weight of iron and the iron-protein complex known as ferritin can readily release the iron into the blood stream. The metal is transported in combination with the beta-1 globulin of the plasma protein and eventually is deposited in the body stores. Here, in the reticulo-endothelial system of the body and especially in the liver and spleen, it remains as hemosiderin and ferritin. Some of the iron reaches the bone marrow and is utilized in hemoglobin production.

The behavior of the iron-beta-1 globulin has been used in determining the activity of the bone marrow and is thus of value as a diagnostic tool. When radioactive iron is incubated with serum or plasma it combines with fraction IV-7 of the protein. This iron-protein when injected intravenously in patients leaves the plasma at a relatively constant rate. The normal time for half of the radioactivity to disappear is about 2 hours; in various blood diseases this differs however (11). From data obtained in blood dyscrasias one can compute the total

turnover of iron by the marrow, the per day formation of red blood cells, the amount used in storage and various other data affording a more dynamic concept of hemoglobin metabolism.

It was believed at one time that the intestinal mucosa excreted as well as absorbed iron. It is now known that except for a small amount appearing in the bile, the body has no means of getting rid of iron. For this reason, patients who have received many transfusions over a long period of time eventually develop a brown pigmentation of the skin since the iron derived from the destruction of red cells cannot be excreted and remains distributed throughout the body and skin as the brown iron-containing pigment, hemosiderin.

The absorption of iron is increased in some anemic states. In normal persons only about 5% of a 300 mg. dose of ferrous sulfate is absorbed. In iron deficiency anemia, as well as during growth and pregnancy, where the iron stores are deficient, as much as 25% of this same quantity of iron is absorbed. It has been postulated that iron absorption is controlled by the intestinal mucosal cell with the following mechanism at work: When the body needs iron, as reflected in depleted iron stores, the plasma globulin bound iron diminishes and in turn calls for iron from the ferritin in the mucosal cell. The resultant apoferritin is then capable of absorbing more iron from the intestine. In normal persons, the apoferritin is nearly saturated with iron and therefore even if large quantities are present in the lumen of the gastro-intestinal tract only little can be accepted and absorbed.

During the war it was of military importance to have whole blood transported to combat areas. It had been known that when citrated blood was stored for a period of one or two weeks hemolysis usually occurred. Even after several days of storage the red cell fragility increased, there was disintegration of platelets and leukocytes and the fibrinogen and prothrombin content fell sharply. Because of this a search was begun for an improved blood preservative.

Ross and Chapin (12) were the first to investigate the problem of the longevity of stored donor red cells after transfusion, by using the isotope technique. They fed ferrous sulfate labelled with radioactive iron, Fe-59, to patients with iron deficiency anemia and this iron was incorporated into the circulating red cells. The blood containing the tagged cells was then collected in sterile isotonic sodium citrate and refrigerated. After storage for varying periods of time, aliquots of blood were transfused into donors and samples removed at intervals. Since the radioactive iron atoms were now part of the hemoglobin molecule, donor cells could be detected in the recipients' circulation as long as the cells remained intact within the blood stream. It was then possible to measure the per cent survival and the rate at which disintegrated cells disappeared from the circulation in the immediate post-transfusion period. The techniques used afforded a high degree of accuracy of measurement. The conclusions arrived at were that red cell survival varied inversely with the time of storage and that sodium citrate was unsatisfactory as a preservative for any period more than 3 days. It was further and incidentally learned that the iron of destroyed transfused erythrocytes is preferentially reutilized for the synthesis of hemoglobin.



Gibson *et al.* (13) systematically studied many different solutions for their value as a blood preservative. These investigators employed essentially the same technique as that of Ross and Chapin but, in addition to the Fe-59, they also used Fe-55. Because the two isotopes have a different pattern of disintegration, the amounts of each could be determined even when present together. The solution found to be the most efficient was acid-citrate-dextrose (ACD), the mixture now used in most blood banks, and which will preserve whole blood for three weeks with 70% viability.

In order to understand more fully the dynamics of pathological states such as shock, heart failure, etc., it has become important to have available an accurate method for the determination of blood volume. One of the best techniques depends upon the use of the dye, Evans-Blue (T-1824) (14). The accuracy of this method is limited, however, because the dye gradually disappears from the circulation in the normal state and especially rapidly and unpredictably in conditions such as shock and burns, where capillary permeability is increased. With the radioactive isotopes of iron and phosphorus, red cells could be tagged and these cells then utilized for blood volume determinations. The chief advantage of the isotope over the dye method is that red cells are not lost from the circulation as a result of increased capillary permeability.

Hahn was the first to demonstrate that when animals are fed radioactive iron, Fe-59, the isotope becomes incorporated in the hemoglobin of the red cell (15). An aliquot of these labelled red cells when transfused into a patient, would mix uniformly throughout the circulation and the blood volume could be determined by the degree of the dilution of the radioactive erythrocytes. This method has not attained widespread use because specially prepared radioactive blood donors must be on hand, fairly large amounts of blood have to be used, and the radioactivity determinations are laborious and time consuming. A much simpler technique was introduced by Hevesy *et al.* using radioactive phosphorus (16). They demonstrated that when human erythrocytes are incubated *in vitro* with P-32, the radiophosphorus is incorporated in the red cell nucleoprotein through enzymatic action and the red cell remains tagged for many hours. As with iron labelled cells, all one need do is reinject a measured quantity of these labelled cells and determine their dilution by the blood. The final radioactivity determinations are comparatively simple and only a few milliliters need be injected. These labelled cells can also be used for studying other problems in cardiovascular physiology, such as cardiac output and residual (17), rate and extent of exsanguination transfusions (18), etc.

The use of radioactive zinc, Zn-65, has increased our knowledge concerning the importance of this trace element in the body economy. When radiozinc is injected into a human subject, it first becomes bound to a fraction of the serum protein. Later it is found within the red and white cells of the peripheral blood. In erythrocytes, the zinc content parallels the degree of carbonic anhydrase activity and probably catalyzes the production of carbonic acid within the red cell (19). A very interesting finding is the markedly increased zinc content of the peripheral white cells in chronic lymphatic and myelogenous leukemia (20).

As the hematologic and clinical picture improves with therapy, such as urethane or x-ray, the zinc content of the white cells concomitantly decreases. Fragmentary as this information is, it nevertheless points a way for future investigation.

When radioactive phosphorus (P-32) is injected into a human, it is distributed throughout the body wherever phosphorus turnover takes place. Maximal uptake occurs where there is increased mitotic activity, as in regenerating liver, bone marrow, and neoplastic tissue (24); eventually it is localized in the bones. The localization in hemopoietic tissue and lymph nodes is two to three times that of other tissues (21). The therapeutic implications of this finds expression in the use of P-32 for some blood dyscrasias.

The treatment of polycythemia vera has always presented a difficult problem. In the past, attempts to bring the blood count to normal have in the most part, been directed at the removal or destruction of blood by phlebotomy or hemolytic agents, such as phenylhydrazine. Since the fundamental abnormality in polycythemia is a hyperplasia of all the bone marrow elements, logical therapy should be aimed at a suppression of this too-rapid erythropoiesis and myelopoiesis, rather than a disposal of surplus blood which has already been produced. Moreover, phlebotomy and hemolysis may in themselves act as stimuli to bone marrow activity. The proof that such therapy is inadequate is revealed by the morbidity and mortality rate in this disease when so treated. In using phenylhydrazine, the end products of erythrocyte destruction are retained within the body, the control of dosage is difficult and without extreme caution, an acute hemolytic anemia may result. Venesection plus a low iron diet, which is given with the hope of decreasing the rate of red cell production, may afford immediate temporary relief, but almost invariably there occurs the production of a large number of microcytic, hypochromic cells. Another unfavorable aspect to phlebotomy is that the sudden removal of a considerable volume of blood in a patient with hypertension, arteriosclerosis or diminished cardiac reserve is not innocuous. Furthermore, despite a reduction in hemoglobin or even in the red count, there may remain a thrombocytosis with the ever-present danger of vascular thrombosis.

Radioactive phosphorus is fortunately uniquely suited for the therapy of this disease. Since the bone marrow is one of the tissues which somewhat selectively concentrates this isotope, some degree of localized radiation may be delivered. The desired result of maintaining a normal blood picture is achieved by the inhibitory effect of the ionization produced by P-32 beta rays on marrow cell proliferation, and with the proper dosage no other deleterious radiation effect is possible. Reports of large series of cases by several investigators (22-25) and our own large clinical experiences with P-32 have convinced us that it is the treatment of choice in polycythemia vera. Recently, Lawrence (26) reported a series of 172 cases followed over a ten-year period. He noted that the expected morbidity due to thrombosis was markedly reduced, and that there was no significant increase in the incidence of leukemia or neoplastic disease. He concluded from the study that a patient with polycythemia vera when properly treated, has a nearly normal life expectancy.

Radiophosphorus is usually administered by intravenous injection, but is just as effective when given by mouth. Due to the variability of phosphate absorption

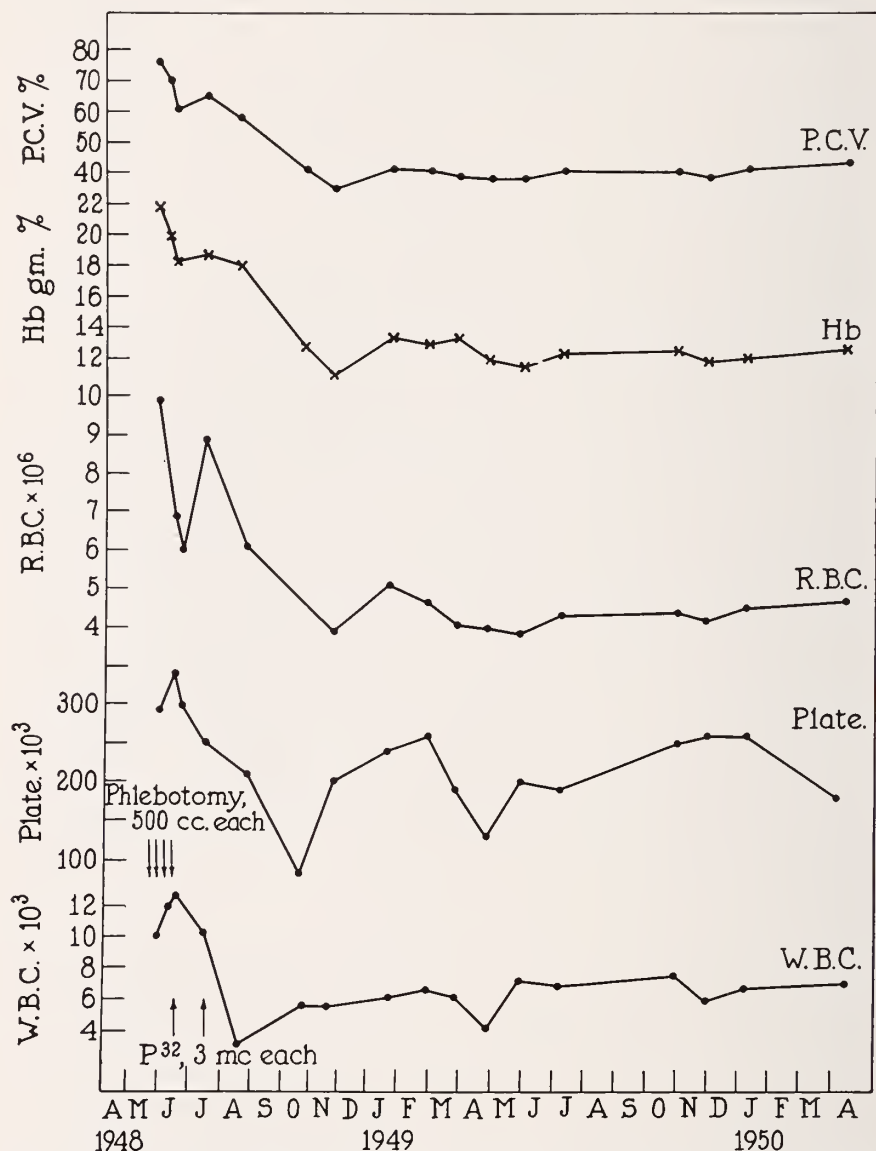


FIG. 1. Polycythemia vera (female, age 67) treated with radioactive phosphorus, with phlebotomy performed initially to reduce the packed cell volume (PCV) rapidly. P<sup>32</sup> may take 1-4 months to produce its effect; therefore this method of treatment is indicated where possibility of interim thrombosis exists. Note a 2 year (to date) remission induced by 6 millicuries of P<sup>32</sup>.

from the gastro-intestinal tract, the oral dose is approximately twice the parenteral.

Treatment of a patient with polycythemia vera is carried out in the following manner: After an examination of the sternal marrow and peripheral blood, 3 millicuries of P-32 are given intravenously. The blood picture is again studied one month later, and if no undue depression is noted, an additional two to three millicuries are administered. No further radiophosphorus is then given for a period of four to five months. Since a patient's response to a given dose of P-32 is extremely variable, a complete blood count must be done each month and the course carefully observed. Usually 3 to 6 millicuries will induce a remission lasting for one or more years (figs. 1 and 2). Occasionally, several injections a

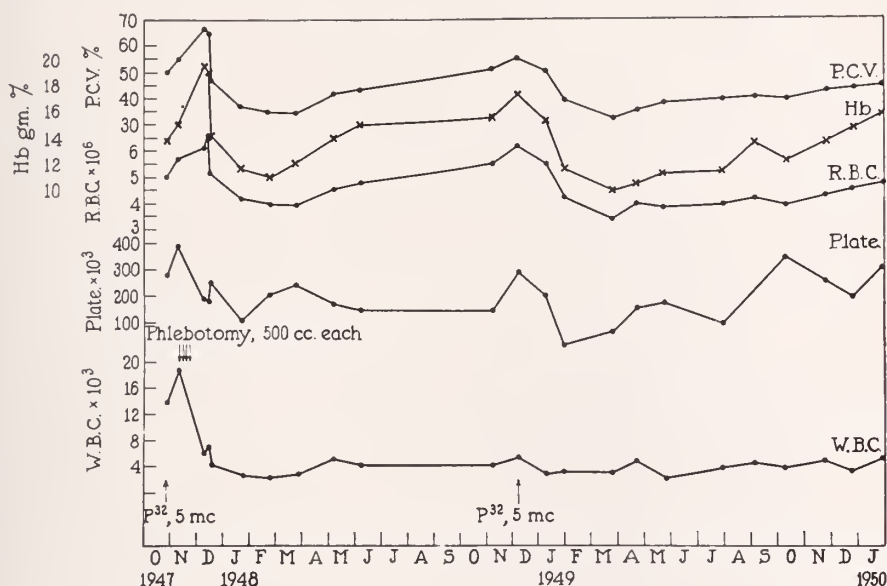


FIG. 2. Response of polycythemia vera to radioactive phosphorus. Radiation effect of  $P^{32}$  on the bone marrow was delayed necessitating phlebotomies one month after the administration of  $P^{32}$  to combat severe symptoms. Note the one year remission to 5 million of  $P^{32}$ ; subsequent relapse responded to a similar dose of radiophosphorus.

year are necessary, while in one exceptional case in our experience it took ten injections totaling 30 millicuries to produce a response. It is evident, therefore, that therapy must be highly individualized in each case, the condition of the patient carefully evaluated, and the course closely followed.

Because of the known good response of chronic leukemia to x-radiation and the demonstration that there is an increased uptake of radiophosphorus in the spleen, liver, bone marrow and lymph nodes of these patients, P-32 has been successfully used as a therapeutic agent in this disease. The advantage over roentgen therapy is the absence of radiation sickness, a milder and more prolonged radiation effect, and a wider tissue dispersion. Lawrence has studied a series of 129 patients with chronic myelogenous leukemia (27), and 100 cases of chronic lymphatic leukemia (28). He concluded that in the latter group the period of comfortable life was prolonged as compared with other methods of



treatment. Similarly, more successful results were obtained in the chronic myeloid type. Our own experience confirms the above views.

A course of P-32 for the treatment of chronic leukemia consists of weekly injections of 1 to 2 millicuries for a period of one to two months. Often, and especially in chronic myeloid leukemia, therapy results in a decrease of the white count with a reduction or a disappearance of immature forms. One does not attempt to cause the white count to return to normal because of the danger of

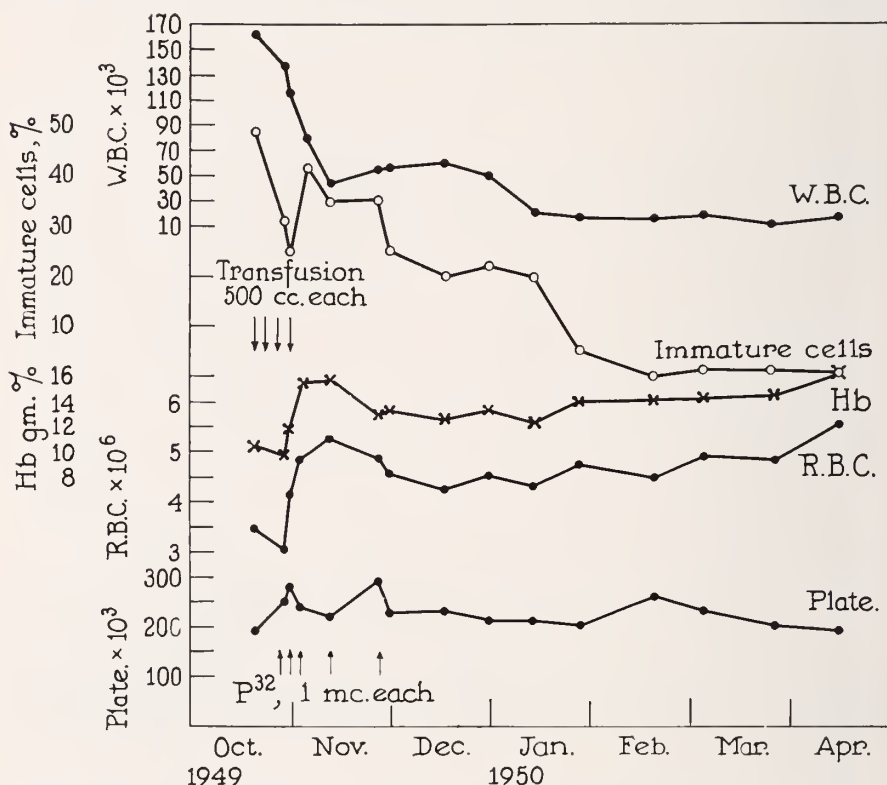


FIG. 3. Chronic myelogenous leukemia treated with radioactive phosphorus. Note rapid drop in white count to nearly normal levels, and the disappearance of immature cells in the peripheral blood. The hemoglobin, red count and platelets are well maintained.

irreversible bone marrow depression. Concomitantly, the hemoglobin rises, the spleen and liver decrease in size, and the patient feels subjectively improved (fig. 3). Sometimes the course of radioactive phosphorus is repeated in several months. As in polycythemia vera, the actual total dose administered is a highly individual matter, and each case should be treated as a special problem and carefully followed with frequent hematologic studies.

Radiophosphorus has been used with some success in follicular lymphoblastoma and multiple myeloma (29). In combination with x-ray and chemotherapeutic agents such as urethane and stilbamidine, cases resistant to any one type of treatment may undergo a temporary remission when two or more of

these agents are employed simultaneously. P-32 has little or no value in the treatment of Hodgkin's Disease or acute leukemia.

Radioactive sodium has also been used in some cases of chronic leukemia (30). Possible advantages to this type of therapy over P-32 are the shorter half-life of Na-24 (15 hours as compared with 143 days for P-32), and the less variable excretion. It is, therefore, somewhat easier to regulate the dosage of radiosodium and treatment may be adjusted to comply with the immediate demand of the patient's symptoms and findings. Because sodium is generally distributed throughout the body, the radiation administered by this isotope is comparable to total body radiation over a 48-hour period. Only a small number of cases so treated have thus far been reported and the results obtained are similar to cases which have received P-32 or x-ray.

Radioactive gold (Au-198), when injected intravenously in the colloidal state, concentrates in the reticuloendothelial system of the liver, spleen and lymphoid tissue (31). For this reason it has been used in such pathologic states as lymphosarcoma, reticuloendotheliosis, leukemia and Hodgkin's Disease. The advantages of this localized radiation are apparent and successful use of this isotope has been reported (31). The relatively short half-life of radiogold makes it more useful as a therapeutic agent for use in humans, where longer lived isotopes are to be avoided. It appears likely that radiogold colloid may be of value in the treatment of splenomegaly resistant to other forms of therapy.

Other colloids with varying particle size have been prepared. Since the localization is to some extent dependent on the size of the colloidal particles, it may eventually be possible to prepare colloidal compounds with affinity for any one of a number of specific organs. Thus far, colloids of chromic phosphate (32) and yttrium and zirconium (33) have been used in humans, either as tracers or as therapeutic agents in the treatment of neoplasias, leukemia and polycythemia.

Radioactive strontium has also been used in multiple myeloma (29) and bone carcinomas (34). Experience with this isotope is still limited, but some relief of pain and improvement in the clinical condition have been observed.

Radioactive isotopes have proved valuable tools in hematologic research and it is hoped that as compounds with a high degree of selective localization are discovered, more efficient therapy of the leukemias and lymphomatous diseases will be possible.

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# X-RAY DIFFRACTION ANALYSIS OF MIXTURES CONTAINING SODIUM SALTS OF FATTY ACIDS\*

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In the study of skin excretions, the quantitative analysis of mixtures of homologous fatty acids poses several problems for the analytical chemist. Additional difficulties arise when the material to be analyzed is available in micro-amounts only.

The composition of the fatty secretions of the human skin is not well known. Sweeping a skin area with defatted cotton yielded samples of only a few milligrams even after pooling of several cases; moreover, these samples consisted for their greater part of skin debris, while only a small portion was soluble in organic solvents. Equally scanty samples were obtained from comedones, e.g. in cases of *acne vulgaris*. We, thus, faced the necessity to resort to microanalytical procedures for the study of the chemical composition of the fat components in such excretions. While engaged in a study by chromatography and by frontal adsorption analysis, we wished also to explore the efficacy of X-ray diffraction for the microanalysis of such mixtures. Crystalline materials, irradiated with X-rays cause diffraction phenomena that are characteristic of the compounds in the sample. This method has been used extensively for analytical applications (1), because it is nondestructive for the sample and may be carried out with very small specimens (1–5 mg.).

X-ray diffraction data are available for a number of homologous series of aliphatic compounds; for the fatty acids themselves (2, 3), their silver salts (4), their amides (4, 5), and their anilides (4, 6). The cross section of aliphatic chains, being of uniform dimension, causes the short spacings, usually designated  $d_2$  and  $d_3$ , to be almost constant for each series. The long interplanar spacings ( $d_1$ ) vary in direct proportion to the number of carbon atoms in the chain. This then provides a method for identifying individual fatty acids through their characteristic long spacings. The longest axis of the crystal unit, derived from the innermost line of the diffraction pattern, is longer than the chain length of one molecule and one can assume that it corresponds to the projection of the double length of the molecule.

As the fatty acids in skin excretions occur not only in the free state, but also as soaps and in the form of various esters, such as glycerides, phosphatides and cholesterol esters, they could be most conveniently and economically isolated as the sodium salts. This form of sample offers additional advantages in the case of the lower volatile acids.

In order to establish the usefulness of the procedure it was necessary to pro-

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vide a number of standard reference diagrams from known samples. We therefore prepared a series of pure sodium salts from propionate to stearate. It has been shown that the sodium soaps may exist in various crystalline phases (7), depending on the method of preparation and the degree of hydration. Since this would tend to confuse the interpretation of the X-ray diagrams, all specimens were prepared and handled in the same manner.

Propionic, valeric, caproic, heptylic and pelargonic acids were purified by distillation *in vacuo*. The middle fraction after checking of the acid equivalent was neutralized by titration with normal sodium hydroxide and the solution evaporated to dryness under an infrared lamp. The resulting soap was dried to constant weight in the Abderhalden pistol at 100° in a vacuum of 0.2–0.5 mm. Commercial samples of sodium propionate, butyrate and caprylate were obtained from Mycoloid Laboratory, Inc., of Little Falls, N. J. We are obliged to Drs. L. Shedlovsky and J. Ross of Colgate-Palmolive-Peet Co., of Jersey City, for pure samples of the sodium salts of capric, lauric, myristic, palmitic and stearic acid, prepared according to Miles and Ross (8). All these sodium salts were dried under the conditions described above.

The X-ray diffraction specimens were prepared by sealing small quantities of the finely powdered soaps into thin-walled (0.03 mm.) pyrex capillary tubes, 1.5 cm. long and about 0.75 mm. outside diameter. The higher members of the series have a tendency to flaking; thus, it became increasingly difficult to fill the capillaries. The sealed capillary type of specimen was employed in order to avoid changes in the sample due to atmospheric contact during the course of the lengthy exposures.

According to Bragg's Law,  $\lambda = 2 \frac{d}{n} \sin \theta$  (where  $\lambda$  = X-ray wavelength,  $\frac{d}{n}$  = interplanar spacing and  $\theta$  = Bragg angle). Thus, long spacings (large  $\frac{d}{n}$  values) correspond to small  $\sin \theta$  values. This requires the use of a small angle camera. The film-to-specimen distance (which controls the minimum measured angle) varied from 10 cm. for the lowest members of the series to 25 cm. for the highest (C<sub>18</sub>) soaps. A copper target X-ray tube was used with a nickel filter to remove the  $\beta$  radiation. The exposure times were of 10 hours duration. The data for  $d_1$  are given in Table I. They show arithmetic progression with increasing number of carbon atoms. There is a slight zigzagging between the subseries with an even and with an odd number of carbon atoms.

*Binary Mixtures.* X-ray diffraction has been previously applied to the unraveling of mixtures of homologs. In a case closely related to the present one, mixtures of aliphatic acids have been investigated by Francis, Piper and Malkin (9) and by Slagle and Ott (10). The former group found the  $d_1$ -spacing in binary equimolecular mixtures at the arithmetic mean between the  $d_1$ -spacings of the components; which would indicate the formation of double molecules consisting of one long and one short molecule. This result is not contradicted by the measurements of Slagle and Ott who find, however, a fairly continuous trend for the

$d_1$  spacings of non-equimolecular mixtures for a variety of pairs. This leads them to assume that solid solutions may exist in all proportions. The situation is, moreover, complicated by the superposition of up to four crystalline modifications for each of the fatty acids and, by implication, for their binary solutions. Similar concepts are applied by Slagle and Ott to such mixtures as the five even-numbered acids from  $C_{10}$  to  $C_{18}$ , the four odd-numbered acids from  $C_{11}$ - $C_{17}$  and for a mixture of all nine acids mentioned.

These considerations are not immutably applicable to mixtures of the sodium salts. In the following Table II we give our observations on mixtures of propionate and butyrate in a variety of molecular proportions, also on two different mixtures of propionate and pelargonate. It may be discerned that the equimolecular mixture of propionate-butyrate gives, as the only strong line, one that

TABLE I  
*Long spacings of sodium soaps from small angle X-ray diffraction diagrams*

NUMBER OF CARBON ATOMS	SODIUM SOAPS	SPACINGS ( $d_1$ ) IN ÅNGSTRÖMS
3	Propionate	11.2
4	Butyrate	14.3
5	Valerate	15.4
6	Caproate	18.4
7	Heptylate	20.2
8	Caprylate	23.6
9	Pelargonate	24.2
10	Caprate	27.7
12	Laurate	31.2
14	Myristate	34.7
16	Palmitate	39.5
18	Stearate	42.6

corresponds to a  $d_1$ -spacing which is the arithmetic mean of that of the two components, indicating a fairly perfect double crystal, similar to the findings of Francis, Piper and Malkin and also of Slagle and Ott for equimolecular mixtures of acids. In the case of 3:1 mixtures, the same line is found as in the 1:1 mixture, but the component present in excess displays its typical line separately. In two examples for propionate-pelargonate mixtures, both pure salts are identifiable; in one of them mixed double crystals produce a spacing at  $18.2\text{Å}$ .

In the more one-sided 9:1 mixture of the propionate-butyrate couple both components show up where the salt with the shorter chain is in excess, while in the reverse case the presence of propionate is completely masked—a situation which is unfavorable from the analytical view-point. The 1:9 mixture of propionate-butyrate was subsequently repeated, but this time as a merely mechanical mixture by grinding the dry pure components. Under these conditions, both components present themselves in the diagram. Upon solution of this mechanical mixture in water and subsequent crystallization, the minor component was again masked as in the previous experiment, where the sample had been obtained

by evaporating a solution of the soaps. These findings demonstrate for the case of the sodium salts the existence of certain limits of molecular aggregation below which a minor component of a mixture will escape detection by X-ray diffraction. Similar limits of detectability of 5–10 per cent have been experienced in other instances (1).

*Ternary Mixtures.* A mechanically mixed sample of the sodium salts of the acids C<sub>10</sub>, C<sub>12</sub>, and C<sub>14</sub> in equimolecular proportions yielded lines (see Table III) essentially corresponding to those of the individual components. The arithmetic mean of C<sub>10</sub> and C<sub>14</sub> would of course be indistinguishable from the

TABLE II

*Long spacings of binary mixtures of sodium soaps from small angle X-ray diffraction diagrams*

COMPONENTS		SPACINGS (d <sub>1</sub> ) IN ÅNGSTROMS			REMARKS
Na-pro- pionate Mol. %	Na-buty- rate Mol. %				
90	10	11.3		14.3 W*	Mechanical Mixture The same mixture re- crystallized
75	25	11.5 W	12.6		
53	47		12.9		
50	50		12.8	14.1 MS†	
25	75		12.6 W	14.3	
10	90			14.3	
10	90	11.3 W		14.3	
10	90			14.3	
Na-pro- pionate	Na-pelar- gonate				
66	34	11.3 W	18.2 W	24.3	
50	50	11.2 W	(12.0) W	24.4	

\* = Weak.

† = Medium Strong.

All other spacings obtained from strong lines.

value for C<sub>12</sub>, but in the case of the pairs C<sub>10</sub>–C<sub>12</sub> and C<sub>12</sub>–C<sub>14</sub> no trace was detected at the half-way distance. Mixture of the salts C<sub>8</sub>, C<sub>12</sub> and C<sub>14</sub> in equimolecular proportions presents a more critical situation, since none of the possible arithmetic means coincides with the values of the components themselves. The diffraction pattern of the mechanical mixture shows the values of all 3 pure components, but no other lines. By dissolving this sample in water and evaporating it to dryness a more intimate mixture is achieved. Now C<sub>8</sub>, the shortest member, is masked, C<sub>12</sub> shows the same value, while C<sub>14</sub> is represented by a slightly shorter spacing, perhaps due to change in modification or solid solution.

*Complex Mixtures.* As a complex mixture of biological nature, but available in larger amounts than in skin excretions, we prepared the mixed sodium salts of butter fat. Fifty g. unsalted butter was saponified by refluxing for 10 hrs. with 250 ml. of 2.5 N alcoholic sodium hydroxide. The alcohol was removed by



distillation and replaced by hot water. The unsaponifiable matter was extracted with ether. The fatty acids were freed with sulfuric acid and taken up with

TABLE III  
*Long spacings of ternary and more complex mixtures of sodium soaps  
from small angle X-ray diffraction diagrams*

CHAIN-LENGTH OF COM- PONENTS	SPACINGS (d <sub>1</sub> ) IN ÅNGSTROMS						REMARKS
C <sub>10</sub> C <sub>12</sub> C <sub>14</sub> *	27.3	31.1	34.5				Mechanical Mixture
C <sub>8</sub> C <sub>12</sub> C <sub>14</sub>	23.7 M	30.6	34.6				Mechanical Mixture
C <sub>8</sub> C <sub>12</sub> C <sub>14</sub>		30.6 M	33.3				The same mix- ture recrystal- lized
$\left\{ \begin{array}{ccc} C_4 & C_{10} & C_{12} \\ C_{14} & C_{16} & C_{18} \end{array} \right\}^\dagger$	$\left\{ \begin{array}{ccc} (13.5)\text{MW} & 14.5 \text{ M} & 28.0\text{M} \\ 35.7 \text{ MS} & 39.5 & 42.5 \end{array} \right\}$						Mechanical Mixture
$\left\{ \begin{array}{ccc} C_4 & C_{10} & C_{12} \\ C_{14} & C_{16} & C_{18} \end{array} \right\}$	(13.5)MW	(20.2)M	41.0				The same mix- ture recrystal- lized
“butter soaps”	12.9 MW	19.0 MW	35.7	38.5M	56.0W		

\* All ternary mixtures were equimolecular.

† The components of the more complex mixtures are given in Table IV.

MS = Medium Strong, M = Medium, MW = Medium Weak, W = Weak. All other spacings obtained from strong lines.

TABLE IV  
*Average composition of fatty acids in butterfat and components of "Synthetic Butter"*

FATTY ACIDS OF BUTTERFAT	NUMBER OF CARBON ATOMS	WEIGHT % FATTY ACIDS ACC. TO HILDITCH*	WEIGHT % SYNTHETIC MIXT. (Na-SALTS)	MOLECULAR % SYNTHETIC MIXT. (Na SALTS)
Butyric.....	4	2.6-3.5	5	11.3
Capric.....	10	1.8-3.6	5	6.4
Lauric.....	12	3.2-5.7	10	11.1
Myristic.....	14	6.9-11.1	15	14.9
Palmitic.....	16	22.8-29.1	45	40.2
Stearic.....	18	6.5-12.5	20	16.1
Oleic.....	18	31.3-41.3	—	—
Linoleic.....	18	3.6-5.1	—	—

\* This column contains only the acids occurring in more than 3% ratio.

ether. After concentration the ether extract was neutralized with sodium hydroxide and dried at 60°C. and 0.3 mm. vacuum. The average composition of fatty acids in butter, according to Hilditch (11), is given in the third column of Table IV.

We also prepared "synthetic butter soaps" by mixing the six most frequent saturated components of butter; their corresponding weight and molecular percentages are found in columns 4 and 5 of Table IV.

The spacings given by this mechanical mixture correspond to those of all the individual salts with the two major components palmitic and stearic acids prevailing in strength. The spacing of  $13.5\text{\AA}$  may be due to a higher order reflection. Upon solution and evaporation, the pattern is essentially changed, retaining only a long spacing of  $41.0\text{\AA}$  half-way between stearate and palmitate. The weaker spacings at  $20.2\text{\AA}$  and  $13.5\text{\AA}$  are again ascribed to higher orders.

The natural butter-soap mixture itself, which is comparable to the more intimate mixture, shows spacings near the values for  $C_6$ ,  $C_{14}$  and  $C_{16}$  and a very long spacing at  $56\text{\AA}$ . It should be noted that this natural sample contains a large percentage of oleate.

*Penicillin-Sodium Propionate Mixtures.* In connection with a therapeutic problem it became of interest to decide whether any chemical interaction such as complex formation takes place in solution between penicillin and sodium propionate. Small angle X-ray diffraction of crystalline, penicillin-G, gives a spacing at  $15.7\text{\AA}$ . The combination of penicillin with sodium propionate had to be studied in lyophilized samples. Lyophilized penicillin gives no diffraction pattern, but must be treated with acetone to recover crystalline form. For the same reason, various lyophilized mixtures of penicillin with sodium propionate gave only the spacing of sodium propionate at  $11.1\text{\AA}$ . After treatment with acetone both spacings,  $11.1\text{\AA}$  and  $15.7\text{\AA}$  were observed. The absence of any other spacings excludes the formation of a molecular complex between the two components.

#### CONCLUSIONS

On the basis of our results one may draw the following conclusions:

1. The X-ray diffraction method may be used to identify any number of components in a mechanical mixture.
2. The effect of mixed crystal formation (solid solutions) in samples, obtained by evaporation of dissolved mixtures, causes variations in long spacings, which make positive identification impossible. In mechanical as well as in more intimate mixtures of sodium salts of normal aliphatic acids there is a strong tendency to form double molecules comprising one long and one short constituent. These form not only in equimolecular mixtures, but are also apt to appear in mixtures of varying proportion.
3. Components present in minor amounts may become completely masked, especially if they are the shorter species of a pair. In some cases the spacing of one pure component will be missing, but that of the double molecule will indicate its presence.
4. These findings suggest that the use of X-ray diffraction in the analysis of homologous aliphatic series be limited to mechanical mixtures.

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## ABDUCENS NERVE PALSY FOLLOWING SPINAL ANESTHESIA\*

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The introduction of spinal anesthesia by Bier (1) in 1898 was a natural event in the evolution and growth of medical science. Bier's work was preceded by a number of basic scientific and technical advances which made spinal anesthesia a logical and inevitable development. Thus, in 1825 Magendie (2) described the cerebrospinal circulation. In 1853 Wood (3) developed the modern hollow metallic needle, while in the same year Pravaz (3) invented the hypodermic syringe. The need for a true local anesthetic was filled in 1860 when Niemann (3) isolated the active alkaloid of coca leaves and named it "cocaine". It remained for Carl Koller (4) in 1884 to report on the use of cocaine for local anesthesia. In 1885 Corning (5) experimented on the possibilities of spinal anesthesia with cocaine. The ground was now fertile for the final evolutionary step, the intrathecal injection of an anesthetic agent in patients; this was achieved by Bier. The first reported use of spinal anesthesia in the United States is credited to Tait and Caglieri (6) who in 1899 performed an osteotomy of the tibia with this technique. It is of interest to note that Dr. Albert A. Berg (7) in 1900 employed spinal anesthesia on his patients only to abandon its use later because of untoward effects.

While a voluminous literature has accumulated attesting to the usefulness and wide application of spinal anesthesia, a significant number of papers has appeared describing postspinal neurological sequelae, both transient and permanent, e.g. postspinal headache, transverse myelitis, cauda equina syndrome, peripheral nerve lesions, cranial nerve palsies and chronic arachnoiditis. These sequelae constitute greatest criticism of spinal anesthesia.

It is our purpose to report a case of unilateral abducens nerve palsy, appearing after spinal anesthesia, to discuss the pathogenesis of this complication and to suggest prophylactic measures.

### CASE REPORT

*History.* S. M., (Hospital #606,694), a white male, 67 years of age, was admitted on January 21, 1950 with the complaints of progressive dysuria and urinary frequency. His family and past histories were unimportant. The patient was a well developed and well nourished male. Examinations of the head, neck, heart and lungs were negative. On abdominal palpation the urinary bladder was found to be two fingers above the pubic crest. The rectal examination showed the prostate to be diffusely enlarged, some three times greater than normal. A bladder residual of 300 cc. was found.

On January 24, 1950, a suprapubic cystotomy was performed under spinal anesthesia. The anesthetic agent used was pontocaine (14 mg.); this was mixed with .5 cc. of 10% glucose and diluted further with cerebrospinal fluid to a total volume of approximately 3.5 cc. The size of the spinal needle used was either 20 gauge or 22 gauge. There were no technical difficulties experienced in performing the lumbar puncture. The operation was performed without mishap and the patient was returned to his bed in good condition.

Twenty-four hours later the patient complained of severe frontal headache, accentuated

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by the erect position and relieved by recumbency. The headache continued for the next 7 days and was associated with considerable nausea and some vomiting. There was no evidence of meningeal irritation. The total fluid intake on the operative day was 1620 cc.; during the next 3 days the fluid intakes were 2880 cc., 2520 cc., and 2460 cc. Fluid output was satisfactory. Profuse diaphoresis was present postoperatively for several days. The headache was treated with mild analgesic drugs.

On the sixth postoperative day, the patient complained of double vision. He was seen by a consulting ophthalmologist; examination showed an inability to abduct the right eye. The eyelids, pupils, fundi, visual fields and intraocular pressure were normal. A diagnosis of right abducens nerve palsy was made.

On February 6, 1950 a suprapubic prostatectomy was performed under gas-oxygen-ether anesthesia. The operation was uneventful. The postoperative period was stormy; auricular fibrillation and congestive heart failure appeared. On the seventh postoperative day the patient suddenly expired. The abducens nerve palsy remained without change up to the time of death.

#### DISCUSSION

Cranial nerve palsy after spinal anesthesia is an uncommon occurrence. In 1947 Thorsen (8) reviewed the world literature and collected 324 such cases; of these 299 involved only the abducens nerve, while in 8 a simultaneous injury to another cranial nerve (II, III, IV, V, VI, VIII and XII) was present. In the remaining 17 cases some cranial nerve other than the sixth was involved (III, IV, VII, VIII and XII). According to Thorsen, whose monograph "The Neurological Complications of Spinal Anesthesia" (8) is the most complete work on the subject, the incidence of abducens nerve palsy after spinal anesthesia is .25%.

This complication appears unilaterally in 75% of the cases, more often on the right side, and is most common in males below the age of 50. Classically, it appears 7 to 8 days following a spinal anesthesia or lumbar puncture. According to Greene *et al* (9) it is constantly preceded or accompanied by a typical postspinal headache. There is, as a rule, no associated meningitis. While the palsy practically always disappears within a few weeks, permanent diplopia has been reported (10).

The pathogenesis of abducens and other cranial nerve palsies after spinal anesthesia has been a subject of considerable speculation. Levine (11) lists the following causative factors suggested by various workers: 1) elective toxic action, 2) localized hemorrhage, 3) mild meningeal infection, 4) irritation of the meninges by the catabolic products of the anesthetic agent, 5) loculated collection of cerebrospinal fluid at the base of the brain and 6) some mechanical or toxic factor in patients with a hysterical or neuropathic constitution.

These theories have little concrete support. There is little evidence that a bacterial or chemical toxic plays a causative role. The toxic theory does not explain why cranial nerve palsy may appear after a diagnostic lumbar puncture. Also, the concentration of the anesthetic agent when it reaches the cranial cavity, if it does at all, must be considered ineffective. Johnston and Henderson (12) have shown that direct application of anesthetic agents to the fourth ventricle fails to produce such cranial lesions. As for the suggestion that meningeal infection or irritation serves to cause abducens nerve palsy, it is significant to note that clinical evidence of meningitis is usually absent when this nerve in-

vovement appears. Instead of an increased cerebrospinal fluid pressure, as would be expected with a meningitis, there is observed a hypotension (13, 14, 15).

Greene and coworkers (9) have noted and emphasized the constant association of headache with postspinal cranial nerve palsy. This strongly suggests some common causative factor. The evidence supports the theory that both postspinal headache and cranial nerve palsy result from a post-puncture hypotension of the cerebrospinal fluid and a resulting disturbance in cerebral statics (8). Also, the evidence indicates that this postspinal hypotension results from the leakage of cerebrospinal fluid through the dural puncture hole into the epidural space (16, 17). This theory of pathogenesis of postspinal cranial nerve palsy has been admirably presented by Thorsen (8) as follows: "At the decrease in the quantity of cerebrospinal fluid, which is the result of lumbar puncture, the filling with cerebrospinal fluid in the basilar subarachnoidal spaces is reduced in an erect position. The weight of the cerebrum will then not be compensated by a displacement of fluid to the same extent. The relative weight of the cerebrum will increase and, as a result of this a gravitation will take place in a caudal direction. Thus, the prerequisites are created for traction on the cerebral nerves and the sixth nerve, in particular, and with it for the occurrence of a local pressure against prominent formations. This type of cranial nerve injury is therefore not a manifestation of a local process, in the actual sense, but of a dislocation of the cerebrum, irrespective of the phenomenon causing the dislocation."

Wolff (18) notes that in the presence of cerebrospinal hypotension there occur both intracranial venous dilatation and increased bulk of the brain and suggests that these factors add further to the alteration in cerebral statics.

The vulnerability of the abducens nerve in any disturbance of cerebral statics is so well known that it has been called "the weakling of the cranial contents" (19). It will be recalled that after the abducens nerve emerges between the lateral part of the pyramid and the lower border of the pons, it runs in the posterior cranial fossa about 15 mm. and pierces the dura over the basi-occiput. Under the dura it runs up the back of the petrous portion of the temporal bone where it is held in a groove. Upon reaching the sharp upper border of the petrous temporal bone it bends sharply (almost at 90 degrees) under the superior petrosal sinus and petrosphenoidal ligament and enters the cavernous sinus. Thus, the abducens nerve is more or less anchored to the pons and to the cavernous sinus; gravitation of the cerebrum in the caudal direction will result in pressure of the abducens nerve against the sharp upper border of the petrous temporal bone (19).

If the genesis of postpuncture cranial palsy as previously presented by Thorsen is correct, then the prophylactic measures to reduce the incidence of this complication should be directed towards 1) the prevention of continued leakage of cerebrospinal fluid through the dural puncture hole, and 2) the increased formation of cerebrospinal fluid.

1. Since the size of the dural puncture hole determines, to a major degree, the extent of cerebrospinal fluid leakage, it follows that fine gauge needles be used. Antoni (20) in 1923 stressed this point and described his fine caliber needles. Greene *et al* (21) have revived our interest in the use of fine needles, the 24 and

26 gauges. In a report of the 24 gauge needle, these workers had a postspinal headache incidence of only 2.5 per cent, in contrast to the control group (with 22 gauge needle) which showed an incidence of 26 per cent. In a series of 700 cases, in which the 26 gauge needle was used, Greene (27) showed a headache incidence of .4 per cent. Another aid in minimizing the size of the puncture hole is the technique of directing bevel of the spinal needle laterally. Since the fibers of the dura run primarily in a craniocaudal direction, a laterally directed needle will form a smaller opening than a needle whose bevel is pointed cephalad or caudad (8). Another factor in reducing the amount of leakage of spinal fluid is the horizontal position. Prolonged recumbency may conflict with the present day practice of early ambulation. We favor the use of the horizontal position in the immediate post-operative period until active motion or ambulation are begun. The use of 26 gauge needles may eliminate completely the need of recumbency.

2. The importance of increasing the formation of cerebrospinal fluid is apparent from our discussion of the pathogenesis of postspinal cranial palsy. Weed and McKibben (22), Solomon (23) and Alpers (24) have demonstrated the value of intravenous hypotonic solutions in the treatment of postspinal headache and in the restoration of lowered cerebrospinal pressure to normal levels. Conversely, Masserman (25) reported the aggravating effect of intravenous hypertonic fluids on postspinal headache. Wolff (18) produced immediate and complete relief of post lumbar puncture headaches with intrathecal physiological saline administration. Greene et al (21) showed a statistically significant reduction in postspinal headaches by an increased oral fluid intake, specifically 10 glasses of water a day for 2 days. Therefore, in the absence of specific contra-indications, a patient should receive the benefit of increased fluid intake during the first 2 postoperative days. The oral route is preferred as in the regime suggested by Greene et al (21). Where the parenteral route must be used, 5 per cent glucose in distilled water to provide a minimum total intake of 3000 cc. a day should be administered. It is of considerable interest to note that in the case being reported the fluid intakes on the operative and immediate postoperative days were deficient.

When a postspinal headache has appeared, active definitive measures must be taken to correct the hypotension of the cerebrospinal fluid lest a cranial nerve palsy appear. The measures should include 1) constant recumbency until the headache disappears in the erect position, 2) forcing of fluids in order to establish a positive fluid balance and increase the formation of cerebrospinal fluid, and 3) the use of posterior pituitary extract, 10 units every 12 hours for three doses, because of its antidiuretic effect. Recently, Asbell (26) recommended the use of intramuscular desoxycorticosterone, 5 mg. in 1 cc. of sesame oil, in postspinal headache, because of its action in increasing extracellular fluid and plasma volumes. Asbell's interesting report has yet to be confirmed.

#### SUMMARY

A case of unilateral abducens nerve palsy following spinal anesthesia is reported. The pathogenesis is discussed. Prophylactic measures against this complication are suggested.

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# BALLISTOCARDIOGRAPHY\*†

## A REVIEW

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The ballistocardiograph may be defined as a device for recording the movements imparted to the body by the recoil of the heart and movement of the blood, or the forces generated when these movements are restrained. Interest in these movements has grown considerably in the past ten years largely through the persistent efforts of Isaac Starr who has written extensively on the subject. Prior to Starr's entrance into the field, only sporadic reports appeared in the literature. In a recent review (1) he has cited some of the earlier efforts. In 1877 J. W. Gordon suspended a bed from the ceiling and obtained a record of its motion synchronous with the heart beat. In 1905, Yandell Henderson published records obtained from a suspended table and also was the first to suspect that they were related to cardiac output. In 1913 Thomas Satterthwaite obtained records of a patient sitting on spring scales. In 1922, Heald and Tucker devised a technique using an electrical method which, however, did not record the direction of the deflections. In 1928 Angenheister, a geophysicist, obtained records from a seismograph placed next to a table on which subjects were resting. In 1933 Abramson published records from an elaborately and delicately constructed chair and proposed a formula for calculating cardiac output from the records obtained. His formula, however, has not proved to be applicable to curves obtained from apparatus in use today.

At the present time, there are three types of apparatus in use: 1) the high frequency undamped ballistocardiograph designed by Starr and Rawson; 2) the low frequency, critically damped ballistocardiograph designed by Nickerson and Curtis; 3) the simplified types of apparatus for recording movements directly from the body, as described by Dock and Taubman. In the construction of a ballistocardiograph, it has been found necessary to have the natural frequency of the bed or table as far as possible from the natural frequency of the body lying on it. This is to prevent the movements generated by forces within the body from being either augmented or extinguished by being constantly in or out of phase with the natural movements of the table. The normal frequency of the body (cadaver) is about 6 cycles per second. Starr built his machine with a high frequency of about 15 cycles per second. The apparatus consists of a thin, 3-ply panel of braced plywood suspended by wires from the ceiling. Lateral motion is prevented by movable struts attached to the wall, and longitudinal motion is opposed by a strong steel spring. The spring is mounted on a rigid welded steel

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structure, screwed to the floor and braced against the walls. A mirror is attached to the spring itself and pivoted on the spring support so that movements of the table impart movements to the mirror. A light beam directed against this moving mirror permits optical recording of the table's movements on photographic paper, magnified 8,000 times. No special damping device is used, the lower rate of the body's natural frequency providing all the damping needed. The spring of the apparatus is adjusted so that a static force of 280 grams displaces the image of the reflected light beam one centimeter.

The apparatus constructed by Nickerson and Curtis (3) has a natural frequency of 1.5 cycles per second, much slower than that of the human body. The ballistocardiographic bed is also critically damped so that oscillations produced by one cardiac beat do not interfere with each other or those of the next beat. The bed consists of a board, supported by four long heavy flat and adjustable steel springs, damped by a light metal sylphon bellows damper, and recorded electronically. Nickerson and Curtis believe that the low frequency bed provides more accurate tracings because high frequency recording instruments overaccentuate by resonance and other factors the high frequency components of the cardiac cycle to the detriment of the lower frequency events more closely related to the cardiac stroke. Although theoretically the low frequency apparatus may be better, practically it has one disadvantage in that the low frequency of normal respiratory movements interfere with the oscillations of the table to such an extent that subjects must of necessity hold their breath while records are being taken. On the high frequency apparatus, subjects can breathe normally.

Recently Dock and Taubman (4) have demonstrated three techniques for recording ballistocardiograms directly from the human body. The first, a sphygmographic method, employs a standard Cambridge Simplitrol pulse recording device. The movements are picked up from the subject's head by either a glycerine capsule or a receiver made by mounting a piece of cork button 3 cms. in diameter on a rubber membrane 5 cms. in diameter. The second, a photoelectric method, records variations in electric current produced in a photoelectric cell by movements of a shadow cast by a piece of cardboard, metal, or occulting edge attached to a subject's head or shins. The third, an electromagnetic method differs from the second in that a coil of fine copper wire is substituted for the occulting strip and an Alnico magnet is substituted for the photoelectric cell. A galvanometer attached to the coil inscribes a ballistocardiogram through variation in current produced by movements of the wire in the electrical field. Although attempts at standardization have been made, Dock feels that the curves inscribed by the ballistocardiograph are more suited to clinical application as empirical indices of disease than for precise physiological measurements of function. His simple little devices should open up this field to a much larger group of investigators than has been possible up to the present time.

Several other forms or modifications of the ballistocardiograph have been described. Starr and Lawson (5) have constructed vertical and chair ballistocardiographs. Krah1 (6) has built an apparatus in which impulses are picked up from a standard platform scale. Brown and Pearson (7) have modified the optical recording device described by Starr by building an electronic dual recording

apparatus for simultaneous recording of ballistocardiogram and electrocardiogram.

Many other minor variations in the above techniques are possible. One which we have used employs the sphygmographic method described by Dr. Dock. To overcome some of the lag inherent in the Simplitrol pulse recorder, we have converted the mechanical energy picked up by the glycerine capsule into electrical energy by means of the Sanborn Electromanometer and inscribed records with the electrocardiograph string galvanometer. Such a record is clear, well defined and resembles in every way the recordings obtained by Starr (fig. 1).

*The Normal Ballistocardiogram.* Despite the differences in types of recording

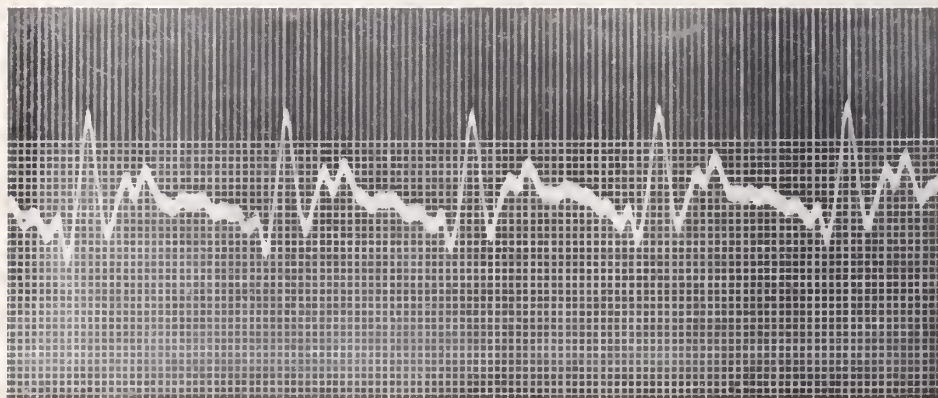


FIG. 1. Ballistocardiogram taken directly from the subject's head with a glycerine capsule, converted into electrical energy with an electromanometer and recorded with the electrocardiograph string galvanometer.

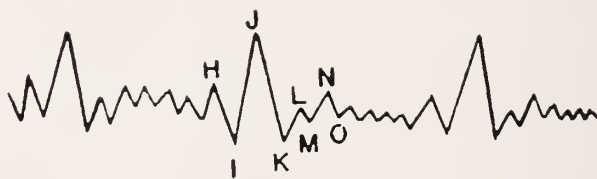


FIG. 2. Normal Ballistocardiogram

apparatus, the form of the ballistocardiograms obtained by different methods are actually quite similar. A normal curve is depicted in Figure 2.

At the beginning of electrocardiographic systole, the body moves headward a little producing the H wave (2). This wave is produced by the acceleration footward of the heart itself during auricular contraction and the period of isometric ventricular contraction. In complete heart block, in those ventricular contractions where there is no immediately preceding auricular contraction, the H wave is usually absent (8). The larger footward movement, the I wave, occurs at, or shortly after, the onset of ejection, and represents the recoil of the heart as it ejects blood into the aorta and pulmonary arteries (2). This is not dissimilar from the recoil of a gun. Hamilton, Dow and Remington (9) have pointed out after comparison with simultaneous pulse tracings that this wave occurs actually a fraction of a second later than it should if it represents the cardiac recoil but



account for this by the time necessary to neutralize persistent forces set up during the H wave. The largest headward movement, the J wave, is produced by a combination of factors including the impact of blood against the aortic arch and against the bifurcation of the pulmonary artery, the acceleration footward of blood in the aorta and the deceleration of blood in the heart (2, 9). The largest footward deflection, the K wave, is often even larger than the J wave. It represents a summation of forces produced by the after fling of the aorta (2), and the impact of blood against small arteries in the lower part of the body (9). It occurs simultaneously with the peak of the femoral pulse wave. Nickerson and Curtis (8) using a model heart and aorta have shown that the depth of the K wave is proportional to the length of the aorta.

The smaller waves following the K wave are called by Starr "diastolic waves" or "after vibrations" (2). He has not attempted to identify them with specific impacts in the cardiac cycle. These waves are not recorded on the low frequency, critically damped ballistocardiograph. Hamilton *et al.* (9) have suggested that the L wave is caused by slowing of blood in the ascending aorta, the peaks occurring at the time of closure of the aortic valves. The footward movement the M wave representing a thrust against the aortic valve, N an after fling, and O the development of a diastolic pressure wave in the lower extremity. Against this argument that the diastolic waves represent active surging of blood in the aorta, Starr has demonstrated that the movements are not very different from the vibrations of a cadaver (10).

In the normal ballistocardiographic tracing the size of the impacts increases with each inspiration, to diminish again as the subject exhales (2). The H waves, on Starr's ballistocardiograph (11), vary in height depending on the phase of the vibrations. The amplitude of these vibrations depend on whether or not the impulses are delivered in phase. The HI segment is sharp and clearly defined. HI and IJ make acute angles with the vertical and they occur in the first half of systole. The J peak dominates the record. There are more variations in amplitude of the K wave than the other prominent waves. In most records, L and M are the most prominent diastolic waves, although it is not uncommon for N to be higher than L. None of the diastolic waves approach the amplitude of the I, J, and K waves. The lines connecting the H, I, and J peaks are nearly straight and notches or slurs are not seen. JK, straight in most records, may have a conspicuous notch when the rate is slow.

*Some Theoretical Considerations.* It has been noted (11) that the size of the initial I and J waves is related to the cardiac output and that the form of the ballistocardiogram is determined by the shape of the curve of blood velocity in the great vessels. Thus, when the circulation is feeble, the ballistocardiogram will be of low amplitude, and when the heart is weak, the form of the ballistocardiogram will be altered. In order to try to make interpretation of curves something more than empirical observations, Starr *et al.* (2, 5, 10) and Hamilton *et al.* (9, 12) have demonstrated mathematically how the form of the ballistocardiogram is related to the shape of the cardiac ejection curve. For mathematically disinclined physicians the explanation given by Starr in his 1947 Harvey Lecture (1) is easier to understand. The movements of the body, it has



been shown, are related to movements of the blood; as blood in the ascending aorta accelerates headward the recoil drives the body footward (arrow 1, figs. 3A<sub>2</sub> and 3B<sub>2</sub>). The acceleration of blood in the descending aorta a moment later is represented by Arrow 2. Since this mass is larger than that in the ascending aorta, the arrow is made larger. The slowing of blood in the ascending aorta and descending aorta are represented by Arrows 3 and 4. The velocity or ejection curve plotted in 3A indicates that the blood normally accelerates more rapidly than it decelerates. The converse is seen in 3B, where the slow acceleration and rapid deceleration of the weak heart is represented. It is because of these differences that Arrows 1 and 2 are made larger in 3A<sub>2</sub> and Arrows 3 and 4 are larger in 3B<sub>2</sub>. The shape of the ballistocardiogram can be determined by connecting the

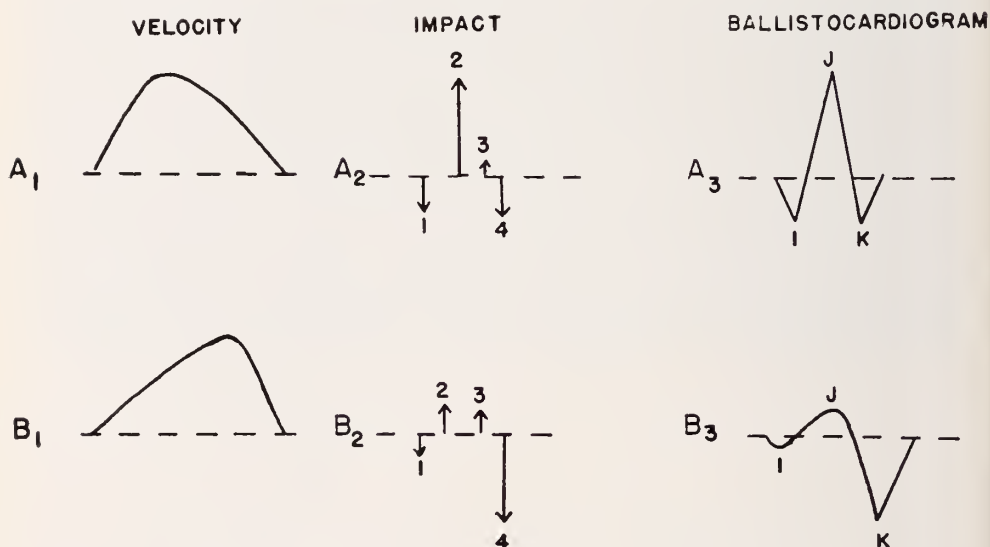


FIG. 3. Diagrammatic representation of the origin of the Ballistocardiogram (after Starr (1)).

tip of the arrows. A<sub>3</sub> is a normal curve. B<sub>3</sub> shows a shallow, obtuse I wave, a low amplitude, delayed J wave, and a deep, late K wave. This latter type of curve is not infrequently encountered in heart disease.

Starr and Friedland (13) have studied the variation in ballistic amplitude occurring with respiration. No change in the patients' position on the ballistocardiographic table alters the normal inspiratory increase in amplitude and expiratory decrease. Thus changes in position of the heart and diaphragm themselves are not factors in this phenomenon. On the other hand, breathing by positive pressure will reverse the normal sequence indicating, therefore, that it is related to intrathoracic pressure changes. In observing a patient with a ventricular aneurysm the J wave was seen to have two peaks, the first being due to the right ventricle, the second being due to the left ventricle. This second wave is delayed because of time necessary for the aneurysmal sac to distend before sufficient pressure is built up for ejection to occur. During inspiration J<sub>1</sub> is larger

than  $J_2$  but during expiration  $J_2$  is larger than  $J_1$ . This demonstrates the better filling and output of the right heart on inspiration and of the left heart on expiration. It, too, can be reversed by positive pressure breathing. The drop in left ventricular output during inspiration is further demonstrated by the drop in blood pressure and pulse pressure which occurs at that time. It is seen, therefore, that although the total record reflects more the output of the left heart the fact that ballistic amplitude increases in inspiration indicates that respiratory changes affect the right side of the heart predominantly. Only in this way can the rise in amplitude during inspiration be explained.

*The Ballistocardiograph as a Means of Measuring Cardiac Output.* The applicability of the ballistocardiograph to measuring cardiac output stems from consideration of the law of conservation of momentum. In other words, the change in momentum of the blood must equal the recoil momentum of the body. Since momentum equals mass  $\times$  velocity, if the form of the pulse wave is unvarying, the mass of blood moved (Stroke volume) should be related to the velocity of the moving ballistocardiographic bed as well as to the ballistic throw or displacement. Thus records obtained either electronically, which record velocity of displacement or optically which record amount of displacement, will provide a method for calculating Stroke volume.

Formulas which have been derived for calculation of cardiac output or stroke volume have been partly empirical—to best fit in with the results obtained by older methods—and partly mathematically derived. Starr (2) from a knowledge of the shape of the normal ejection curve derived two formulas. The first is  $Sv = 7\sqrt{(3I + 2J)AC^{3/2}}$  where  $Sv$  = Stroke volume in cc.  $I$  and  $J$  are the height of those waves measured in millimeters from the base line,  $A$  = the cross section of the aorta in square centimeters and  $C$  = the duration of the cycle in seconds.  $A$  is calculated from tables published by Bazett. The second is an integral formula  $Sv = 33\sqrt{\left(2 \int Idt + \int Jdt\right)A\sqrt{C}}$ . In this formula  $\int Idt$  and  $\int Jdt$  is the area under the respective waves in mm. seconds. Both these formulas hold only for a normal cardiac ejection curve and thus for only normal ballistocardiograms. They apply only when the apparatus is built according to the specifications and is standardized according to the methods of Dr. Starr. A correction is made in measuring the height of  $I$  and  $J$  in that  $I$  = height  $I$  minus 40 per cent height  $h$ , and  $J$  = height  $J$  minus 40 per cent height of  $I$ . This is to correct for rebound overshoot inherent in the apparatus. According to Starr (11) the normal cardiac output, as obtained by this method, ranges between 18 and 29 cc. per minute per pound. The chances are 97.5 per cent that any values above or below these values are abnormal.

Cournand, Ranges and Riley (14) compared the results of the normal ballistocardiogram and a direct Fick method in measuring the cardiac output in man. The Stroke volume by the direct Fick averaged 18.5 per cent larger than that calculated from a simultaneous ballistocardiogram with extremes of +10.6 per cent and +33.5 per cent. In checking the estimated aortic diameters with actual

diodrast measurements they found that Bazett's figures were too low. Using actual measurements, the results between the two methods checked to within 3.5 per cent of each other. Although Starr is at present at work on a new formula eliminating A, it has been suggested that results found by ballistocardiogram be corrected upward by the 18.5 per cent error found experimentally.

In cases of shock, Courmand *et al.* (15) found that there was a significant difference between the ballistocardiogram and the direct Fick. In all cases the ballistocardiogram gave false high values. They suggest this may be due to 1) diminution of the capacity and therefore the cross section of the aorta because of the marked decrease in blood volume, or 2) a relative increase in ejection velocity as compared with normal conditions. This latter assumption has support in the change in contour (sharp initial peak) for the pressure curves in conditions with diminished filling of the arterial system.

Nickerson (16, 17) has similarly derived several formulas for the calculation of cardiac output using the low frequency critically damped ballistocardiograph.

One of these formulas is  $Sv = 5.02 \frac{FP}{TL}$  where F = the force represented by the height of the J wave, calculated proportionally from a known displacement of the table produced by a weight of 35 grams. P = the square root of the arithmetic mean of the systolic and diastolic blood pressure, T = the time interval between peaks of I and J waves, and L = the height of the subject in centimeters. The constant 5.02 was chosen to best fit results with the direct Fick method. In checking with the direct Fick (17) the cardiac output obtained by ballistocardiograph fell within 25 per cent of that obtained by catheter technique in 87 per cent of normals and in 80 per cent of all types. Though the correlation in normals was not as good as Starr's, this technique permitted use in shock where Starr's did not. In both methods the presence of aortic insufficiency made results much too high, reflecting total amount ejected and not accounting for the amount of regurgitation.

The advantages of the ballistocardiograph in determining cardiac output lie in its simplicity of operation, the ease with which prolonged and repeated observations can be made, and the lack of any physical or mental trauma to the patient. It seems to be especially adapted for making repeated observations to detect changes in the same patient and in running acute experiments where even beat to beat changes in output are of interest. Numerous acute experiments have been made. For example, Hardy and Godfrey (18) studied the effect of intravenous fluids on cardiac output in dehydrated patients and in normal subjects. Both groups were given fluids at the rate of 20 cc. per minute until 2500 cc. were administered. The cardiac output of the dehydrated patients increased from -12 per cent below average normal to +30 per cent. The six normal subjects showed no change. The increase in the dehydrated patients accompanied an increase in blood volume and was found to be due to an increase in stroke volume. The controls all had a diuresis and no significant change in blood volume occurred. Segers and Walsh (19) injected 50 cc. of 50 per cent glucose into normal subjects and cardiacs and found that a rise in cardiac output

of between 10 and 30 per cent lasting for five minutes occurred in the normals but that an average increase of 40 per cent, lasting 15 or 20 minutes occurred in the cardiaes. They attributed this difference to a direct effect of glucose on the myocardium. Numerous other studies on the effects of drugs (20), of hemorrhage and intravenous gelatin (21) of pressure breathing at different simulated altitudes (22), etc., have been made.

Starr (23) has also used the ballistocardiogram to test "coordination" of the circulation by studying the circulatory adjustments necessary to prevent pooling of blood in the lower extremities on arising from the recumbent to the standing position. The normal cardiac output shows an average increase of +1 per cent, ranging between +29 per cent and -27 per cent. If in the upper normal in the recumbent position the tendency is for output to drop on arising. The reverse is true for those subjects with low normal output in the recumbent position. Patients with abnormal coordination show exaggerated changes and tend to be inconsistent in their reactions. It was found that patients with mild ill health increased their cardiac output on arising in order to maintain normal circulation. If this was not sufficient, muscular trembling occurred in the lower extremities to prevent pooling in the legs, and if this too was insufficient syncope occurred. In advanced heart disease, increase in cardiac output may not be possible so that incoordination downward was encountered most frequently in this group. In neurocirculatory asthenia, there was a tendency for cardiac output to rise on standing.

The disadvantages of the ballistocardiograph in determining cardiac output have also been long recognized. They stem from the fact that the apparatus cannot be attached directly to the heart and that, therefore, the form of the curves obtained is altered by parts of the body, clothing, bedding, table, pick up units and recording device. Each distortion depends on its natural frequency of vibration and inherent damping. In addition, the output cannot be determined where cardiac disease has distorted the ballistocardiographic curves, in shock, in the presence of severe dyspnea, tremor or during exercise (10). Both Dock (4) and Hamilton (12) have stated that there can be no simple correspondence between force curves of the ballistocardiogram and the stroke volume because of the fact that the curves depend on velocity rather than on volume alone and because there are so many complexities in the manner in which the forces are produced. Hamilton recommended that investigation take an empirical and descriptive trend rather than one based on oversimplified mathematics.

*The Significance of Abnormal Ballistocardiographic Patterns.* Ballistocardiographic patterns may vary from the normal in three ways. The amplitude may be too high, it may be too low, or the form itself may be altered. To standardize techniques of taking records, Starr (11) suggested taking "basal" records after 15 to 30 minutes of rest, and not less than two hours after a meal. Paine and Shock (24) found that the ingestion of a meal raised cardiac output 12 per cent for  $3\frac{1}{2}$  hours following eating, and thus recommended that basal records be taken after a fast of at least  $3\frac{1}{2}$  hours and preferably  $5\frac{1}{2}$  hours.

The syndromes of subnormal and supernormal circulation have been well



studied and described by Starr (25, 26) and Starr and Jonas (27, 28). The syndrome of subnormal circulation which is manifested by low ballistic amplitude and low calculated cardiac output has been termed hypokinemia; that of super-normal circulation, where ballistic amplitude is increased and cardiac output is high has been termed hyperkinemia. The normal cardiac output is 23 cc. per minute per pound of body weight  $\pm 22$  per cent. The normal limits are 18 cc. and 29 cc. Thus, any record which gives a calculated output of more than 29 cc. reveals an hyperkinemic circulation; any record which gives a calculated output of less than 18 cc. reveals an hypokinemic circulation.

Hypokinemia is seen in all moribund patients, in all patients in shock, and in all with myxedema. Almost all patients with chronic angina pectoris have it as do most patients with heart failure. Three-fourths of those patients convalescing from severe febrile illnesses and many with pituitary or adrenal disease show it. Hypokinemia is seen in half the patients with valvular disease not in failure and in half of those who have recently had a myocardial infarction. It is seen in hypertension in about one-third of the cases. In a series of 100 patients, 26 cases had no known cause, and were thus termed cases of "essential" hypokinemia.

Hyperkinemia is seen in almost all cases of hyperthyroidism; it is seen in most cases of patent ductus arteriosus, and in three-fourths of patients with extreme emaciation. (This last is relative, the calculated cardiac output being normal for the normal body weight.) Hyperkinemia is also seen in one-fourth of the patients with anemia, and a few each of healthy persons, patients with peripheral A-V aneurysms, patients with hypertension when associated with cardiac hypertrophy, and patients late in the course of a febrile illness; it is seen occasionally in chronic pulmonary disease and after pneumonectomy. Twenty cases in a series of one hundred were termed "essential" hyperkinemia.

The clinical picture of essential hypokinemia and hyperkinemia is very interesting. Both usually occur in young adults and both think themselves nervous. Both are frequently labeled as neurocirculatory asthenia or psychogenic cardiovascular reaction. Those with hypokinemia complain of weakness, dizziness, light-headedness in the upright position, fainting attacks, dyspnea on exertion and easy fatigability. Those with hyperkinemia have no weakness or fainting and only slight dyspnea, but complain chiefly of tachycardia, palpitations, loss of weight and are often suspected of hyperthyroidism. In a series of 68 cases with the above symptoms, 46 (about 70 per cent) had either hypokinemia or hyperkinemia. Of the 22 other cases, 7 were in the very low normal group, 11 who had only attacks of symptoms, had definite neuroses, and four showed a peculiar increase in ballistic impacts and heart rate on rising from supine to standing associated with symptoms of dizziness and palpitations. In none of this group of 68 cases was there any other objective evidence of disease of the cardiovascular system.

The clinical significance of abnormal forms of the ballistocardiogram is becoming more apparent as more patients are studied and long term follow-ups reported. Classification of specific patterns has not been possible as it has in electrocardiography for the simple reason that even in the same patients abnor-

mal patterns vary from beat to beat and with each respiration. Starr (29) has recently made some attempt at classifying records but admits that even when he has gone through the same records a second time his groupings have been different. Care must be taken in reading ballistic records not to mistake artefacts caused by muscular contractions. Only those abnormalities regularly repeated need attention. For identification of abnormal waves, simultaneous electrocardiogram or pulse tracings must be taken.

The most common abnormalities occur in the I and J waves. Any complex is judged abnormal if the I wave is rounded, notched, or flattened and if its area is markedly reduced (fig. 4A). The J wave is abnormal if its peak is rounded, flattened, or notched so that it fails to dominate the record (fig. 4B). A more advanced type of this abnormality has been called the "Late M" type (11) (fig. 4C). In this form it appears as if the notch in the J wave has become bigger extending often beneath the base lines so that the J wave forms the first limb of the "M." Starr believes the form can be explained by assumption that one side of the heart is strong, the other weak, the stronger ejecting blood in the normal manner, produces maximum velocity early in systole, while the weaker, ejecting with difficulty does not produce maximum velocity until late in systole. This abnormality seems to be of serious import.

In many abnormal records the K wave tends to increase in size so that with the additional diminution of the I and J waves it comes to dominate the record. This is known as "the late downstroke" type (fig. 4D). This curve results from an abnormal curve of blood velocity in the great vessels due to the fact that maximum expulsion velocity is not obtained until late in systole (compare with fig. 3B3). This abnormality also indicates serious myocardial dysfunction. Various combinations of abnormal I and J waves and deep K waves also occur.

Occasionally abnormal H waves are seen with increase in amplitude so that it equals the J wave in size. This type of abnormality has been termed the "early M" type (fig. 4E) and is seen most often in hypertension. It seems most likely that it represents increased size of impact produced by movement of heart struggling to eject blood against increased resistance. It is also seen, however, in the absence of hypertension and does not seem to be as serious as the previously mentioned abnormalities (11).

In some cardiac conditions, especially in the presence of elevated venous pressure or in congestive failure, the systolic complexes are reduced in size and the diastolic waves become the most prominent feature of the record (fig. 4F). Presumably, they are due to deceleration of blood returning to the ventricles, indicating, according to Dock (4), that the failing heart fills faster than it empties. It is very common to hear gallop sounds with deep diastolic waves. Dock states there may be deep M waves with protodiastolic gallop and a deep wave preceding the H wave in presystolic gallop. He has also described large L waves as occurring in his tracings particularly in acute rheumatic carditis in children and adults. These are seen also in normal children occasionally. In rheumatic carditis with mitral valve disease the L wave may be larger than the J. These records appear to be similar to the "late M" type of Starr.

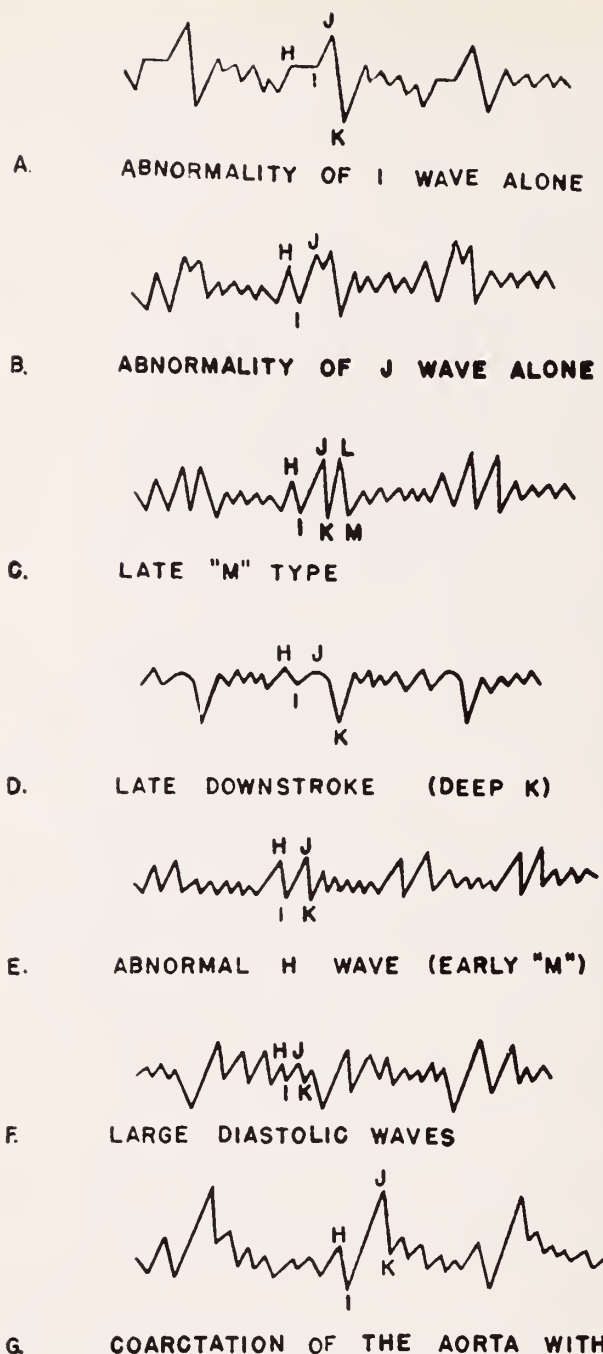


FIG. 4. Various types of abnormality of form

One of the most interesting and characteristic abnormalities of form is seen in coarctation of the aorta where, as one might expect, the K wave is cut off

abruptly at or above the base line (8, 9, 30, 31) (fig. 4G). Following surgical repair, the ballistocardiogram has been noted to return to normal (30, 31). Deep K waves have been seen in uncomplicated hypertension and large H waves and abnormally small K waves following severe hemorrhage and in shock.

In half the abnormal records, the curves are so confused and vary so from beat to beat that no type of abnormality seems to predominate. These records usually occur in the presence of arrhythmias but may occur in the presence of sinus rhythms. Often the form in early or mild cases of heart disease is normal except during expiration when, with poor cardiac filling, abnormalities appear. This latter finding has also been suggested as a means for classifying abnormal records, i.e. according to percentage of complexes which are abnormal (29).

In Starr's experience (29) abnormal ballistic records were found in 50 per cent of patients recovering from coronary occlusion, 45 per cent of patients with rheumatic heart disease, 33 per cent of patients with pericarditis, 29 per cent of patients with cardiovascular syphilis. Following surgical procedures, an increase in ballistic abnormalities over the pre-existing percentage was transiently seen. In a series of 40 cases who showed abnormal ballistic records and later came to autopsy, all but nine showed cardiac abnormalities. Of these nine, eight had only had abnormal records immediately after a surgical operation, the other had advanced pathologic changes in the lungs. Despite the fact that nine patients showed no structural cardiac abnormality at the time of death, Starr believes that the abnormal ballistic records indicated an abnormality of function. Such is seen in both ballistocardiographic tracings and electrocardiographic tracings in normal persons receiving digitalis (32). Also, normal ballistic records are not infrequently seen in cases of organic heart disease. Patients in congestive failure with markedly abnormal ballistic records have been found after compensation with digitalis to show a return to normal of the ballistocardiogram (32). Thus, after compensation, though structural abnormalities persist, functional abnormality is not demonstrable.

In a recent report Brown, Hoffman, and DeLalla (33) found abnormalities of ballistic tracings in all of 37 patients with typical angina pectoris or atypical angina pectoris with other corroborative evidence of heart disease. In thirteen patients with atypical angina pectoris and no other evidence of heart disease, they found abnormalities in 10 patients, none in 3. They concluded that the 10 patients had angina pectoris and that the other 3 had anxiety states. Without sufficient follow-up, this may be a premature judgment, especially since some of their criteria for abnormality are somewhat borderline. (In their first group of abnormal records, the only change was a decreased amplitude of the I-J waves in expiration.)

In addition, Starr and Wood (34) have shown that occasionally patients with known coronary artery disease and mild angina may have normal ballistic records. In fact, they believe that this merely indicates that the disease is mild; they felt also that patients with hypokinemia but normal ballistic form tended to be more incapacitated; and those with an abnormal ballistic curve were by far the most seriously ill. In the acute period following coronary occlusion, independent of the nature of the electrocardiographic changes, the circulation as de-



terminated by the ballistocardiograph may be normal or subnormal. If normal, it tends to diminish and usually reaches a minimum below the normal limit between the third and fifth week. Later, recovery sets in. The left ventricular work which can be calculated from the cardiac output and the blood pressure follows a generally similar course.

The conclusion that the ballistocardiograph is capable of furnishing objective evidence of circulatory abnormality and abnormal heart action in angina pectoris, and even in those devoid of known symptoms or stigmata of cardiovascular abnormality is suggested by studies by Starr. In a study of 8-10 year follow-ups on 90 supposedly healthy patients between the ages of 40 and 85 years, Starr (26) found the following: of 4 subjects who had abnormalities of form, 3 developed objective evidence of coronary heart disease during this period. The 86 others had normal forms. However, the 6 who had the lowest amplitude all developed coronary heart disease. He also found that if one considered those records which indicated a calculated cardiac output 44 per cent or more below the average of healthy young adults, 50 per cent developed serious heart disease. In contrast, only 5 per cent of those above that point developed heart disease. Thus, a ballistocardiogram with abnormal form or of unusually small amplitude may be of serious prognostic significance.

#### CONCLUSIONS

The ballistocardiograph through the limitations which have been described will probably not have wide application as a quantitative research instrument. As a tool for measuring qualitatively changes in cardiac output and in the state of the circulation in the same subject and especially in acute situations, it should have great value. Whether or not the simple direct recording types of apparatus will have value along these lines still remains to be seen. In clinical diagnosis and as an aid in determining prognosis, the ballistocardiograph provides a method for measuring the functional state of the heart, irrespective of the type of organic pathology present.

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# THE CLINICAL PICTURE OF CEREBRAL ARTERIOSCLEROSIS

WITH PARTICULAR REFERENCE TO THE AGED\*

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Increasing knowledge of the pathological anatomy and physiology of the cerebral circulation has made possible a more precise clinical approach to the complex diagnostic problems presented by cerebral arteriosclerosis. For many years this condition has been blamed for nearly every neurologic and psychiatric manifestation occurring in the elderly. Aring (1) states that "cerebral arteriosclerosis *per se* has long enough served the specialist in nervous and mental disease as a faithless crutch". He emphasizes that arteriosclerosis plays an important part in the production of cerebral lesions, but only in conjunction with functional cerebral vascular disorder and with cardiac disease. Since these conditions form the commonplace experience of practicing physicians, a review of their salient clinical features should serve to increase clinical awareness and to encourage diagnostic precision, particularly among the aged.

Arteriosclerosis of the cerebral vessels is the result of the same varied processes that affect the systemic arteries and veins, but is modified by the structure of the cerebral vessels and their location within a box of rigid bone. The sclerotic process in the brain does not, however, necessarily parallel changes in the visceral vessels. In Neubürger's series (2), in fact, only 10 per cent of the cerebral cases showed gross changes elsewhere in the body. On the other hand, if one considered only the group suffering from hypertensive cardiovascular disease, a much higher degree of correlation would be observed.

In older individuals sclerosis of the cerebral vessels is superimposed upon parenchymal and vascular changes which for the present are ascribed to the aging process (3). These changes proceed independently of the arteriosclerotic process and by themselves are held accountable for the progressive impairment of the mechanisms regulating homeostasis, as described by Cannon (4), and also for the gradual onset of impaired vision, hearing, attention, memory, and mental endurance as enumerated by Carlson (5). These structural and functional changes are in turn aggravated by pathological alterations of the arteries and veins. Arteriosclerotic and senescent changes together affect the responses of the cerebral circulation to changing position, to variations in the chemical content of the blood, as well as to changes in intracerebral and systemic blood pressures (6).

Cerebral arteriosclerosis affects tissue nutrition by altering the response of the vessels to neural stimuli, by partially or completely obstructing blood flow as the result of mechanical interference in the form of narrowing, dilatation,

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tortuosity, rigidity, or aneurysm formation of either the gross or microscopic variety. Diseased vessels may rupture, undergo thrombotic occlusion or be closed by embolic particles. In addition they may be the cause of functional insufficiency which manifests itself in transitory disturbances of consciousness, as motor and sensory weaknesses or as paralysis of short duration with complete restitution of function. Such temporary symptoms may be brought about in the presence of cerebral vascular sclerosis by sharp, sudden falls in blood pressure resulting from cardiac disease of many kinds, from hyperexcitability of the carotid sinus, which increases in frequency with age, from spinal and other types of anesthesia, by strong sedatives and by mercurial diuretics. If the condition persists long enough brain damage will result without actual closure of a vessel. Emotional tensions likewise contribute to the disturbance of cerebral circulatory equilibria, but in the presence of organic disease are difficult to evaluate. Acting in a somewhat different way to produce temporary and occasional permanent lesions, are severe anemia, high altitudes, and disturbances of oxygen absorption caused by diffuse pulmonary disease. All investigators agree on the sensitivity of the brain to anoxia of short duration.

Complete functional failure with the establishment of persistent neurologic symptoms occurs as the result of the continued action of the forces just mentioned and also as the result of actual hemorrhage, thrombosis or embolism. The pathogenesis of cerebral hemorrhage has been debated for many years. Globus (7) believes that before an artery ruptures the supporting tissues must undergo degeneration. Others maintain that miliary aneurysms of sclerotic vessels are the site of rupture. In many cases, however, such obvious lesions are absent. Zimmerman (8) found miliary aneurysm in only 75 per cent of his series. Scheinker (9) has described the changes in the veins associated with hypertensive disease of the brain, noting dilatation and congestion, associated with atrophy and degeneration of their walls, which under conditions of increased venous pressure lead to hemorrhages of varying extent.

The syndromes of the specific anatomical localities of the brain have been well worked out by the neurologists and neuropathologists. These include the clinical pictures produced by involvement of the anterior, middle, and posterior cerebral arteries, the basilar artery and its branches, the superior cerebellar, the anterior inferior and the posterior inferior cerebellar vessels. The lenticulo-optic branch of the middle cerebral was called by Charcot "the artery of cerebral hemorrhage", since it supplies the internal capsule, involvement of which produces the typical picture of hemiplegia. Noteworthy, however, is Zimmerman's observation (10) that in some 107 cases of hemorrhage this artery was involved only 38 per cent, the remainder occurring in sites supplied by other vessels. Of particular importance is the fact that many vascular lesions occur in relatively silent areas where well defined symptoms and signs are absent.

The thalamus is considered to be affected in the pseudo-emotionalism which occurs usually in individuals who have suffered strokes affecting opposite sides of the brain. Senile paraplegia was at one time ascribed to spinal cord arterio-sclerosis but is now known to be due to a variety of lesions affecting the cere-

brum (11). Wilson (12) differentiates arteriosclerotic Parkinsonism from post-encephalitic Parkinsonism and from true paralysis agitans.

Lesions caused by vessels supplying the pons and medulla are of particular interest to the internist because of certain obvious changes in ocular movements and because of involvement of the vagus nucleus with consequent dysphagia and cardiac irregularities. At times one sees sharply circumscribed lesions due to involvement of finer branches. Weinstein and Dolger (13) have recently described the external ocular palsies occurring in diabetes mellitus, and emphasized that the neurologic lesion is not related to the age of the patient or the severity of the diabetes but is related to the duration of the disease. Larson and Auchincloss (14) reported 3 cases of multiple symmetric bilateral cranial nerve palsies in patients with unregulated diabetes mellitus associated with polyneuropathy of peripheral nerves. We have recently observed 2 non-diabetic patients, a normotensive man of 75 years, and a hypertensive woman of 84 years, in whom diplopia suddenly developed as a result of 6th nerve palsy, without other neurologic symptoms, and in whom partial restoration of function took place over a period of weeks.

Focal lesions of an entirely different type may occur as the result of direct pressure by hardened blood vessels upon the brain substance or upon the cranial nerves. Such sclerotic arteries may be the site of an aneurysmal dilatation. In Dandy's series of 108 patients with 133 cerebral aneurysms (15), 22 or 16.2 per cent were arteriosclerotic in nature. McDonald and Korb (16), as well as Strauss, Globus and Ginsburg (17) found a higher incidence of arteriosclerotic aneurysms. Mitchell and Angrist (18) have emphasized that arteriosclerotic changes are found in the walls of congenital aneurysms and may determine the site of rupture. In Dandy's opinion 30.7 per cent of cases of trigeminal neuralgia are caused by pressure of sclerotic vessels. Winkelman (19) has recently ascribed convulsive seizures in an aged man to "sclerotic and frequently tortuous blood vessels which were bound down to the cortex".

Pressure on the optic chiasm by tortuous rigid internal carotids has been well described by the ophthalmologists and causes a condition known as "pseudoglaucoma", in which optic atrophy with cupping of the disc is found in association with field defects, but without elevation of intraocular pressure. An excellent description of this condition has been given by Lyle (20). In a paper presented before this Society last year by Dr. Max Schenk and myself, we described such a case and emphasized the value of skull roentgenograms in aiding the diagnosis (21). Other arteries which have been found to cause local pressure changes are the anterior cerebral, the anterior communicating, the posterior cerebral, the posterior communicating, the pontine branches of the basilar as well as the internal auditory.

Diffuse lesions of the brain are often small and commonly do not cause clear-cut clinical pictures. Alvarez (22) has recently described the symptoms of "small unrecognized strokes", and gives as common manifestations, in addition to frank personality changes, such complaints as vertigo, pain in the thorax or abdomen, slight bulbar palsy, unexplained loss of weight, diarrhea, pain in the

face and head, and insomnia. He ascribes these conditions to thromboses of small cranial vessels and supports his views by postmortem correlations. Accuracy of diagnosis in these cases depends largely on careful history taking, bearing in mind the significance of symptoms to which the patient attributes no importance.

Oxygen deficiency may also cause diffuse lesions and an interesting parallel, first pointed out by Cameron (23) may be drawn between the mental reactions of altitude sickness and those of elderly individuals. He has attempted to study the oxygen utilization of the brain of senile patients (24). An excellent review of the effect of anoxia of varying degree on the physiologic processes is available in Van Lier's monograph (25) and is based on the extensive studies carried on during the war on the behavior of pilots. Engel and Margolin (26) have described neuropsychiatric disturbances occurring terminally in chronic asthma and bronchitis as the result of chronic cerebral anoxemia. We have observed nocturnal confusion in old persons as a result of chronic congestive heart failure.

Cerebral symptoms due to cardiovascular disease are commonly encountered in older people because cerebral arteriosclerosis and heart failure increase in frequency with age. The syncope of aortic stenosis and the convulsions of the Stokes-Adams syndrome are well known examples of diminished cardiac output affecting brain function even with normal blood vessels. Rolleston has pointed out that vertigo on exertion may be the only sign of myocardial weakness in the old. In an elderly man suffering from rheumatic aortic stenosis whom I observed for several years, syncope occurred only on unusual exertion, was sudden in onset and cleared quickly without after effects. In congestive heart failure anoxemia may be added to diminished cardiac output to affect cerebral function. In accordance with Scheinker's studies we may also expect increased venous pressure to lead to rupture of diseased cerebral veins.

In acute myocardial infarction the sharp drop in blood pressure may be the first event to affect the brain, but other factors such as emboli and cardiac failure may be operative later. Bean and Read (27) have described a group of cases in which the symptoms indicated acute cerebral disease but autopsy revealed infarction of the myocardium and no acute cerebral lesion. In their cases the bizarre central nervous system manifestations completely obscured the clinical picture. They explain this occurrence on the basis of a fall in blood pressure in the presence of cerebral arteriosclerosis. A similar form of onset in lobar pneumonia was called "apoplectiform" by the older writers and a case of this type is described briefly in a paper on pneumonia in the aged by Wallach and myself (28).

The frequency of cerebral emboli from mural thrombi in the left ventricle in myocardial infarction has probably been underestimated and may easily be overlooked if the brain symptoms occur shortly before death. Dozzi (29) studied 66 patients with hemiplegia for the incidence of coronary thrombosis and found that 8 or 12.1 per cent also had coronary thrombosis which would have been missed had not detailed heart studies been routinely carried out without regard to history or clinical findings. In a woman of 72 years observed at the



Home for Aged and Infirm Hebrews the occurrence of auricular fibrillation at the time of a cerebral insult led to serial electrocardiographic studies which disclosed the progressive changes of infarction.

In subacute bacterial endocarditis brain symptoms may arise from acute cerebral arteritis as a result of bacteremia or from septic emboli. In a woman of 67 years, included in a series of subacute bacterial endocarditis cases in the aged which I studied, the presence of an acute hemiplegia ascribed to cerebral arteriosclerosis diverted attention from her fever, heart murmur and splenomegaly so completely that the endocarditis was only disclosed at necropsy (30).

That hyperexcitability of the carotid sinuses increases with age has been noted ever since the original observations of Weiss and Baker (31). The cerebral type of response to sinus stimulation is usually reversible but in the presence of cerebral arteriosclerosis may have disastrous results in the form of permanent brain damage as pointed out by Marmor and Saperstein (32), by Askey (33), by Zeman and Siegal (34), and by Brannon (35).

Regarding hypertensive cardiovascular disease, I wish only to remind my readers that cerebral complications account for death in about 20 per cent of such cases of all ages. Hicks and Black (36) studied the relation of cardiovascular disease to apoplexy in 155 cases with autopsy. They found hypertension in 90 per cent and concluded that intrinsic functional vascular disease of the brain is the major factor in the pathogenesis of infarction and hemorrhage. Page and Taylor (37) have studied the signs and symptoms useful in younger patients in distinguishing hypertensive patients who will suffer stroke from those who probably will not. If a patient has any 4 of the following signs, they believe that the onset of a stroke within two years is probable: severe occipital or nuchal headaches; vertigo or syncope; motor or sensory disturbances, such as tingling paresthesias; transient paralysis, nosebleeds, or retinal hemorrhages in the absence of papilledema or exudates. Tennent and Harman have reported a study of the factors that affect the prognosis of cerebral vascular accident. They emphasized age, duration of coma, type of respiration, and elevation of blood pressure as being of value. "The type of accident is also important since 30 per cent of hemorrhages and 7.5 per cent of thromboses are fatal in the first attack" (38). Russek and Zohman (39) in a study of hypertensive encephalopathy and cerebral arteriosclerosis have concluded that the cerebral symptoms are aggravated by measures to decrease blood pressure and advocate the use of vasodilators.

The foregoing discussion has aimed to clarify the ways in which cerebral arteriosclerosis may be implicated in focal and diffuse cerebral conditions, many of which are systemic in nature. While it is perfectly proper to postulate the presence of cerebral arteriosclerosis as a causative agent, it should not be invoked as the only one until a painstaking search has been made for possible precipitating forces which have disturbed existing cerebral circulatory equilibria. If we train ourselves to think in terms of cerebral arteriosclerosis plus one or more additional factors, and systematically seek out the unknown, better understanding and more precise diagnosis will be achieved. With aged individuals,



however, the diagnosis of arteriosclerosis comes to mind first and may be clung to for want of a better explanation. Among the conditions that always must be ruled out as simulating vascular disease of the brain are drug reactions, nutritional deficiencies, traumatic lesions and brain tumors, both primary and metastatic. Naumann (40) described a glioblastoma of the occipital lobe simulating psychosis with cerebral arteriosclerosis in an octogenarian and pointed out that the increasing longevity of the state hospital population favors the occurrence of diseases rarely observed in advanced age. Psychoses such as reactive depressions and febrile deliria may be aggravated in the presence of cerebral vascular sclerosis. Space does not permit a detailed discussion of each of these conditions but I would like to emphasize the dangers of overdosage with sedative drugs in the presence of diseased cerebral vessels, to remind internists of the need for looking for a history of trauma in cases of sudden or gradual unconsciousness in the aged, and to point out that cerebral neoplasm may closely resemble a vascular brain disorder as described by Strauss and Globus (41). Gross and Bender (42) have also discussed massive hemorrhage in brain tumors.

Modern methods of investigation are of great assistance in the differential diagnosis. Roentgen examination of the skull, electroencephalography, cerebral arteriography, and studies of cerebral blood flow and oxygen consumption must be employed in addition to the careful use of accepted clinical procedure. These studies will be requested only by the clinician who has learned to be dissatisfied with the facile, off-hand diagnosis of cerebral arteriosclerosis. From time to time his efforts will find reward in a clear cut indication for therapy that will bring real benefit to the patient.

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## THE TREATMENT OF NEUROBLASTOMAS<sup>1</sup>

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The neuroblastoma is a rare malignant tumor which occurs predominantly in infancy and childhood. It is characterized by a rapid course and high mortality, but occasionally by an unusual life history. The tumor arises from primitive cells of the sympathetic nervous system. It is therefore widely distributed. The neuroblastoma has been found mainly in the abdomen where it may arise in the medulla of the adrenal gland, in the celiac ganglion, in the lumbar sympathetic ganglia, in the pelvis, or in the small intestine from Meissner's and Auerbach's plexuses. The tumor may also originate in the thorax, usually in the retropleural region from dorsal sympathetic ganglia. It may arise in an intervertebral foramen and thereby produce a dumbbell-shaped mass with one component in the spinal canal and the other component in either the dorsal spinal muscles or the retropleural or retroperitoneal plane. Other less common locations are the neck, scapular region and thigh where neuroblastoma may arise from the regional sympathetic plexuses. Some authors consider the retinal neuroblastoma in the same category and therefore include the retina as a site of origin, but Willis strongly maintains that the retinal tumor has an entirely different origin and is not a neuroblastoma. The one common denominator of all these sites of origin is the presence of sympathetic nerve tissue, and the most frequent site of origin is the adrenal medulla.

The tumor itself varies greatly in size. It may attain huge dimensions, causing abdominal distention, or it may be so small as to be missed on palpation. The tumor is highly malignant, grows rapidly, invades neighboring structures and metastasizes early and widely by both lymphatic and hematogenous channels. It metastasizes to regional lymph nodes, liver, lungs, bones, meninges, and soft tissues. Metastatic deposits in the retrobulbar soft tissues with consequent proptosis, either unilateral or bilateral, and subcutaneous deposits, especially in the scalp, are peculiar characteristics sometimes described as the Hutchison syndrome. Metastases to the bones are widespread, often symmetrical, and are characterized by both destructive and proliferative changes. Practically all the bones may be affected. Not infrequently the diagnosis may be made by bone marrow aspiration. Massive involvement of the liver in a rapidly growing tumor is frequently described as the Pepper syndrome.

Histologically, the tumor is very cellular. Rosettes and neurofibrils may be seen in the majority of cases. Wright first called attention to the distinguishing histological characteristics of this tumor. The essential cells are more or less undifferentiated nerve cells or neuroblasts (sympathoblasts) which are the formative cells of the sympathetic nervous system, including the medulla of the adrenal gland. The cells are generally small with round nuclei rich in chromatin. The cytoplasm is scanty with delicate fibrils of considerable length. These cells may form

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ball-like aggregations which on section appear as a circular arrangement of one or more rows surrounding a central mass of filamentous processes. This arrangement has been called a rosette, and it occurs not only in the neuroblastoma but also in sympathetic ganglia at certain periods of fetal life. The sympathoblast, which matures into the sympathetic ganglion cell, is the cell of origin of the malignant neuroblastoma, while the mature ganglion cell is the characteristic cell of the benign ganglioneuroma. The maturation of the sympathoblast into the mature ganglion cell is sometimes observed in the neuroblastoma. Not infrequently, areas of differentiation into ganglion cells are present and the finding of these differentiating areas has a special significance in the explanation of the occasional spontaneous maturation of the fast-growing malignant neuroblastoma into the slow-growing benign ganglioneuroma. Willis is of the opinion that every ganglioneuroma originates as a neuroblastoma and then undergoes maturation. Hemorrhage and necrosis are also common findings in the neuroblastoma and may explain the rare spontaneous disappearance of this tumor without treatment.

Of all tumors arising from sympathetic nerve tissue, the neuroblastoma is the most frequent.

The incidence of neuroblastoma is about equal in males and females. The tumor has been found in whites, negroes, and native Mexican Indians. The great majority of these tumors developed in infants and in children under the age of 5 years. In Wittenborg's series of 73 cases, 80 percent occurred before the age of 5 years with 32 percent in the first year of life. Some of the tumors were congenital in origin. The tumor, however, has been found in older children and rarely, in adults. There is no evidence for any familial or hereditary characteristic except for the neuroblastomas of retinal origin.

In the literature, a number of synonyms may be met with, such as neuroblastoma sympathicum, sympathicoblastoma, neurocytoma, sarcoma of the adrenal gland, and similar terms.

Although the tumor is rare, there being altogether about three hundred cases reported in the literature, Farber states it is the most common malignant neoplasm of the abdominal cavity in childhood. In a 10 year period ending in 1939, Farber found 40 cases of neuroblastoma out of a total of 301 cases of tumors in childhood. Of these 40 cases, 32 were in the abdominal cavity. During the same period of time there were 30 cases of Wilm's tumor.

Prior to the publication of Farber's paper, the outlook for neuroblastoma was generally hopeless. Cures were very rare. Lehman reported a 15 year survival of a single case operated upon when the patient was an infant. On the other hand, the radiosensitivity of these tumors was well known and a number of authors, Hauser, Chandler and Norcross, reported cases in which the tumor disappeared after moderate doses of radiation, of the order of 1000 to 2500 roentgens, only to recur later in the same or in another location and eventually to cause death.

In Farber's series of 40 cases there were 10 survivals without evidence of disease from 3 to 8 years after histological verification by exploratory surgery. This means a cure rate of 25 percent which is quite at variance with previously

published reports. More recently, Wittenborg reported a 30 percent survival rate of three or more years.

A study of some of the "cured" cases may shed some light upon those factors which favor cure.

The transformation of a malignant neuroblastoma into a benign ganglioneuroma was actually observed in a case reported by Cushing and Wolbach. A paravertebral swelling at the level of D-6 occurred in the back of a 2 year old child. The child suffered from a paraplegia as a result of this tumor. On exploration, the lesion proved to be a neuroblastoma which was mistaken at the time for a sarcoma. The tumor had apparently originated in an intervertebral foramen and extended into the spinal canal and into the spinal muscles. The father of the child was a physician and, under the direction of the senior Coley, administered Coley's toxins in several courses for a few years. The growth activity of the tumor subsided and the child developed normally except for the paraplegia which persisted unchanged. Ten years later, because of the persistent paraplegia, an exploratory laminectomy was done. The operation disclosed a relic of the former growth which histologically had become completely differentiated into ganglion, capsular, and neurilemma cells. The original slide was re-examined and the diagnosis of neuroblastoma confirmed. This case clearly illustrates that a sympathetic neuroblastoma may mature into a ganglioneuroma.

Ladd and Gross reported that in a retroperitoneal neuroblastoma, which was removed surgically from a 2-year old child, there was histological evidence of maturation into a ganglioneuroma. At the time of operation, no metastases were found and no other treatment was administered. The child was followed for six years and showed no evidence of recurrence of the tumor.

Further evidence of this interesting phenomenon of maturation is found in the not infrequent association of neuroblastoma with ganglioneuroma either in different tumors in the same patient or in the same tumor, as illustrated in the following case:

#### CASE REPORTS

*Case 1. History.* S. F. (596389), a 3½ year old boy was admitted to the pediatric service of the Mount Sinai Hospital on May 16, 1949 for investigation of a shadow in the right lung field first noted 9 months previously on a routine chest x-ray examination. There were no symptoms referable to the chest. The child had been under care since birth for congenital glaucoma. On examination, there were only the physical findings of congenital glaucoma of the right eye and congenital hydrophthalmus of the left eye. The urine was negative. The blood picture was normal. The blood Wasserman was negative. The sedimentation rate was normal. The bone marrow was normal, on aspiration. X-ray examination of the chest (fig. 1) revealed a fairly sharply outlined hemi-spherical shadow to the right of the mediastinum; it was adjacent to the posterior chest wall and extended from the level of the 4th to 8th ribs posteriorly. The appearance was most suggestive of a neurofibroma. X-ray examination of the skull, orbits, and long bones showed no abnormalities. X-ray examination of the cervical spine revealed enlargement of the intervertebral foramen between C2 and C3, particularly on the left. These changes were interpreted as caused by neurofibroma.

Surgical exploration of the mediastinum was performed by Dr. Aufses on June 18, 1949. The right pleural cavity was entered through a posterior circumscapular incision with removal of sections of the 5th, 6th, and 7th ribs. A tumor mass, 3 in. in length and 2 in. in

width, was found in the posterior mediastinum. After separation of a few filmy adhesions, the mediastinal pleura was entered. The mass was then seen to consist of 2 lobules. The superior lobule was soft, reddish purple, and easily separated and removed from the lower lobule. Pathological examination by frozen section revealed a malignant tumor. The lower lobule had the gross appearance of a ganglioneuroma. It was densely adherent to the vertebral bodies and had 3 prolongations into vertebral foramina. It was removed with as much



FIG. 1. *Case S. F.* Roentgenogram of the chest taken before surgical exploration showing hemispherical mass extending from right upper mediastinum.

of the prolongations as possible. Histological examination of the excised surgical specimen (102022) was reported by Dr. Otani as "Ganglioneuroma with areas of neuroblastoma."

Nine days after operation, a course of x-ray therapy directed to the mediastinum and right thorax was begun. The radiation was given through a single posterior field. A dose of 2900 roentgens (measured in air) was delivered over a period of 18 days. The estimated dose in the depth was 1900 roentgens. On September 19, 1949, an x-ray examination of the chest (fig. 2) revealed no abnormalities except for post-operative rib defects. Examination on June 1, 1950 revealed no evidence of recurrence.

#### COMMENT

While the evidence is limited, the maturation of a malignant neuroblastoma into a benign ganglioneuroma is a phenomenon to be reckoned with in the prognosis of this disease.

Another unusual "cured" case reported by Ladd and Gross was that of a 6 week old male infant in whom an inoperable retroperitoneal tumor was found on abdominal exploration. A specimen for biopsy was taken and nothing further was done. The tumor subsequently disappeared without any treatment. The child was alive and well  $8\frac{1}{2}$  years later. In Wittenborg's series, 2 patients with localized tumors and no evidence of metastases were alive and well 12 and 16



FIG. 2. Case S. F. Roentgenogram of the chest taken 3 months after removal of the tumor and 2 months after completion x-ray therapy showing no abnormality of heart, lungs, or mediastinum. Healed rib defects are present at operative site.

years after operative and histological confirmation of the diagnosis. A third patient whose tumor was originally localized to the abdomen died with metastases 10 years after the diagnosis was established. In explanation of these unusual results, one may speculate that either the tumor was destroyed by spontaneous hemorrhage and necrosis or that growth potentiality was inhibited, temporarily or permanently, by maturation.

Among the cured cases reported by Ladd and Gross, there were 2 patients with liver metastases in whom cures were obtained by radiation therapy. The liver metastases were seen at operation and proved by biopsy. One patient was



an infant only 11 days old who was followed for  $3\frac{1}{2}$  years and the other was an infant 3 months old who was followed for 2 years. Wittenborg reported that 6 patients with abdominal neuroblastomas and liver metastases proved by biopsy of a liver nodule survived from 3 to  $12\frac{1}{2}$  years after treatment by radiation only. In still another case reported by Ladd and Gross, a retroperitoneal tumor which extended into the spinal canal was found in a two year old girl. Surgery therefore was incomplete; only the retroperitoneal component was partially removed and the remainder of the tumor left in situ. Radiation therapy was given and the child followed for 4 years, free of disease. These cases prove that neuroblastoma can be cured by radiation therapy even in the presence of metastases, provided, however, that the metastases are closely situated anatomically with respect to the tumor and not distant. This conclusion is further supported by the following case:

*Case 2. History.* C. F. (532802), a one-year old girl was admitted to the pediatric service of the Mount Sinai Hospital on April 4, 1945 for investigation of a left abdominal mass noted by her mother 2 days previously. There were no other complaints. The child had developed normally since birth, and she appeared well developed and well nourished on admission. On examination, a firm, smooth, oval-shaped, fixed mass was palpable in the left upper quadrant of the abdomen. There were no other physical findings. The urine was negative for albumin, sugar, and microscopic abnormalities. The blood picture was normal. The blood Wasserman was negative. X-ray examination of the chest, skull, and long bones revealed no abnormalities. Intravenous pyelography showed a normal calyceal system on the right and compression of the pelvis and calyces of the kidney on the left, but the examination was obscured by intestinal gas. In a roentgenogram of the abdomen, the intestines were displaced by a left upper quadrant mass.

Surgical exploration of the abdomen by Dr. E. E. Arnheim, performed on April 11, 1945, revealed a large retroperitoneal tumor mass in the left upper quadrant. The tumor was bilocular, reddish, partly cystic and partly solid. The anterior portion, 6 cm. in diameter, projected into the peritoneal cavity, while the posterior portion, 12 cm. in diameter, enveloped the left kidney, extended over the pancreas, and extensively involved the retroperitoneal tissues. The tumor could not be removed and was therefore left alone in situ. Large retroperitoneal nodes were seen, separate from the tumor mass and one of them was removed for pathological study. Histologic examination of this node (87988) was reported by Dr. Klemperer as "Lymphnode showing neuroblastoma."

Eight days after operation, a course of x-ray therapy directed to the tumor mass was begun. The radiation was given anteriorly through an abdominal field and posteriorly through a lumbar field. A dose of 1500 roentgens (measured in air) was delivered through each field over a period of 22 days. The estimated tumor dose was 2200 roentgens. The child tolerated the radiation well. On June 1, 1945, the mass was no longer palpable. Subsequent follow-up examinations, including x-ray examination of the chest, revealed no evidence of recurrence. The child has developed normally and is alive and well more than 5 years after operation.

#### GENERAL COMMENT

Surgical excision of the tumor has proved successful, without further treatment of any kind, in 3 of Ladd and Gross's cases and in 7 of Wittenborg's series. These surgical successes were followed for 4 to 16 years without evidence of recurrence.

Wyatt stated that any case of neuroblastoma in infancy and childhood that remains free of disease for one year may be considered a cure. A one year survival in a child is considered equivalent to a 5 year survival in an adult. Ladd and Gross are also of this opinion. Since the average duration of life of the unsuccessfully treated cases of neuroblastoma is only 2 or 3 months, there is some basis of fact to this opinion.

The question may now be asked, what are the conditions or factors which favor cure in neuroblastoma and what is the best method of treatment? Only one factor is common to all the cures described above. That factor is the absence of distant metastases. One must stress the term, "distant," because local or regional metastases to lymph nodes, liver or spinal canal do not preclude the possibility of cure. Wyatt and Farber had treated 10 cases with X-ray, of which 5 were cures and 5 were failures. Of the 5 cures, 2 had local metastases to the liver and yet were favorably influenced by radiation therapy. However, of the 5 failures, 3 had skeletal metastases even before radiation therapy was instituted and the other 2 developed skeletal metastases during the course of treatment. In the literature on this subject, we found numerous case reports in which the primary tumors were favorably influenced by radiation therapy, only to be followed at a later date by metastases to the bones. The impression that one obtains is that the presence of skeletal metastases precludes the possibility of cure. Therefore, every case of neuroblastoma should have roentgenograms of the entire skeleton and a bone marrow aspiration. If there is no evidence of skeletal or other distant metastases, vigorous treatment is indicated. Apart from the unusual phenomena of spontaneous disappearance and spontaneous maturation, cures have been obtained with both surgery and radiation therapy. Surgery is necessary in most cases, if only to establish the diagnosis. Since cures have been obtained by surgery, complete surgical removal of the tumor should be done, if possible. However, radiation therapy alone has also effected complete cures and these successes occurred in cases which were incurable by surgery, cases in which there was fixation of the tumor to the posterior abdominal wall, or liver metastases, or extension into the spinal canal. The indications for radiation therapy are, therefore, in our opinion, much stronger than those for surgery. The cures produced by X-ray therapy have occurred in cases which were much more extensive than those successfully treated by surgery alone.

It is interesting to speculate on what happens to the tumor with X-ray therapy. We know from the work of Glucksmann and Spear on carcinoma of the cervix, that, under the influence of irradiation, a malignant cell may be destroyed directly, or it may be destroyed during a mitotic phase, or it may undergo maturation into a specialized cell which has lost its power of reproduction. Then again, we know from our experience with Wilm's tumors that the marked reduction in size of these tumors which occurs after a course of radiation therapy is caused to a very large extent by hemorrhage and necrosis. We have already experienced some of these phenomena occurring spontaneously in neuroblastoma in the cases of spontaneous disappearance of the tumor and spontaneous maturation into

ganglioneuroma. It is therefore possible that maturation, hemorrhage and necrosis may be major biological effects of irradiation on the neuroblastoma. The irradiation either initiates or hastens biological phenomena which have the "potential" of occurring spontaneously. However, whatever does occur in these tumors under the influence of irradiation, the fact of practical importance is that these tumors can be readily destroyed by radiation therapy. The great majority of failures occurred with skeletal metastases and the widespread nature of the skeletal metastases is the one factor which precludes the possibility of adequate irradiation to all involved areas. The successes with the liver metastases may have been due to the technical possibility of giving adequate irradiation to a limited volume of tissue comprising the primary tumor and the anatomically adjacent liver. The same reasoning holds for the successful treatment of tumors extending through an intervertebral foramen into the spinal canal.

#### SUMMARY

The amazing evidence of the natural history of neuroblastoma indicates a more favorable outlook in the prognosis of this formerly hopeless disease. We can state, with some degree of confidence, that if the disease is limited to one region of the body, even in the presence of local regional metastases, the prognosis is favorable if prompt and vigorous surgical and radiotherapeutic measures are employed. Unfortunately, this disease develops widespread metastases early in its course, and at such a stage the prognosis in our present state of knowledge is hopeless. Therefore, every effort must be made to diagnose these tumors before they metastasize. The "wait and see" method has no place in tumors. Surgical exploration is indicated without delay, if only to establish the diagnosis and to determine the anatomical extent of the tumor. If the tumor cannot be removed completely, a biopsy should be performed, but the surgeon should be able to define the anatomical limits of the tumor with accuracy, so that radiation therapy can be adequately and properly instituted. Radiation therapy should be begun immediately after the diagnosis is established.

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# THE TREATMENT OF PTERYGIUM BY SIMPLE EXCISION

DAVID WEXLER, M.D.

The operation most widely used for many years in the treatment of pterygium consists essentially in transplanting its head, thereby interrupting its growth. Recently attention has been drawn to this subject by D'Ombain (1), Kamel (2), and most recently by Sugar (3). Each of these authors has developed an effective surgical procedure based upon the removal or destruction of the tissues underneath the pterygium.

D'Ombain pointed to the fact that the submucosal part of the pterygium is the active part of the growth, and that some surgeons have dissected and excised the submucosa from the under surface of the conjunctiva before transplanting the head. With this principle in mind, D'Ombain excised the head of the growth, leaving a peri-limbal bare strip of sclera of four millimeters. The subconjunctival area is exposed, and all submucosal tissue as far back as the caruncle removed. His objective is to give the raw corneal surface time to heal before the conjunctiva grows up to the limbus again. Kamel attacked the tissue in the subconjunctival area following its separation from the conjunctival layer, by cauterizing it with phenol. More recently, Sugar introduced a somewhat different conception. He regards the loose subconjunctival tissue beneath the pterygium as a portion of Tenon's capsule. His surgical procedure, with slight modification, is much the same as that mentioned by D'Ombain. The 'tendinous' layer of Tenon's capsule is removed subconjunctivally, the head of the pterygium excised, and as in D'Ombain's operation, a bare area of sclera allowed to remain between the limbus and the conjunctiva overlying the body of the pterygium. An added feature is the insertion of an episcleral suture 3.5 mm from the limbus.

It is my purpose to describe a simple procedure which was suggested many years ago by the late Dr. Isadore Goldstein in which the entire growth is completely removed. It was Dr. Goldstein's belief that the subconjunctival tissue could best be dealt with by removing as much of the conjunctival portion of the growth, consistent of course, with satisfactory approximation of the conjunctival edges of the gap thus created. In this manner, since the greater portion of the subconjunctival tissue is intimately attached to the under surface of conjunctiva, additional dissection or excision of tissue is not necessary to prevent recurrence of the pterygium. In this method, which is applicable to small or moderate sized pterygia, the head is dissected as usual from the cornea. The head and the entire growth with the subconjunctiva are then excised. The decisive step in the procedure consists of the obliteration of the subconjunctival space by means of carefully placed episcleral sutures which bind the conjunctiva to the sclera. Of equal importance, is the accurate suture of the cut conjunctival edge to the limbus by means of an intervening limbal bite.

## SURGICAL PROCEDURE

Anesthesia is produced by one half percent pontocaine drops, and subconjunctival injection of two percent novocaine solution, at the semilunar fold above and below the base of

the growth. The head of the pterygium is grasped on the corneal side of the limbus and shaved from the corneal surface. The free head is then held with mouse-toothed forceps and elliptical incisions are made in the conjunctiva in the growth, or somewhat outside its limbus, above and below (fig. 1). As much as 7 mm. may be safely sacrificed and still adequate closure be assured. A roughly rhomboid-shaped area of bare sclera is thus produced with its widest base at the edge of the semilunar fold (fig. 2). The conjunctiva above

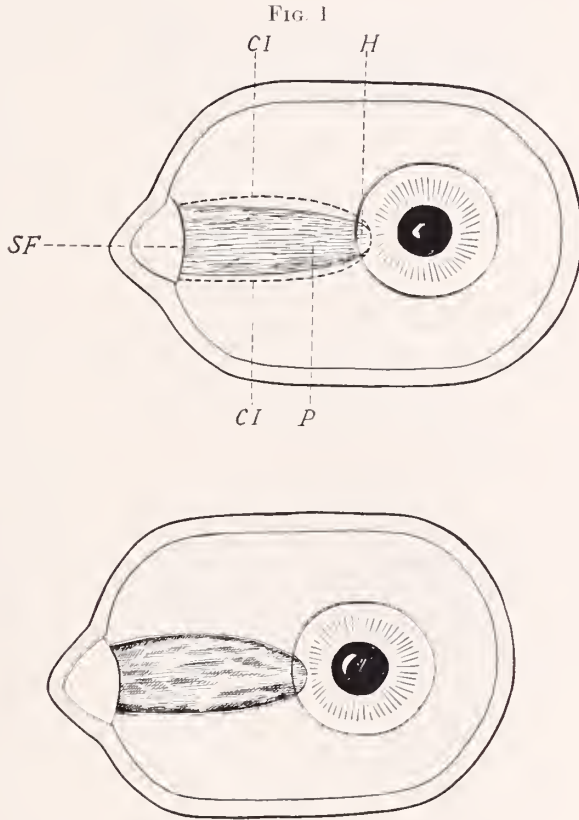


FIG. 2

FIG. 1. The head, H, is dissected from the cornea, and conjunctival incisions, CI, are made along the edges of the pterygium, P, up to the semi-lunar fold, SF.

FIG. 2 Exposed episclera following removal of pterygium

and below are then undermined with seissors for a distance of four or five millimeters. To ensure firm closure at the limbus, the conjunctiva is dissected from the limbus above and below the head for a distance of two to four millimeters, depending on how much is required to ensure accurate approximation. With the aid of sharp pointed fixation forceps a deep scleral bite is taken at a point one millimeter beyond the limbus, using a double-armed silk suture. The free ends of the suture are then passed through the edges of the conjunctival flaps freed by the releasing incisions described (fig. 3). Three double-armed silk sutures are inserted in the sclera, and passed through the cut edges of conjunctiva (fig. 4). The assistant approximates the cut edges of conjunctiva while the sutures are firmly tied, (fig. 5) three knots being made. Finally, the limbal conjunctival episcleral suture is tied with the help of the assistant who holds the conjunctival edges in place. A separate suture for the somewhat gaping wound at the semilunar fold is not necessary. The eye is patched, and sutures removed on the fifth day.

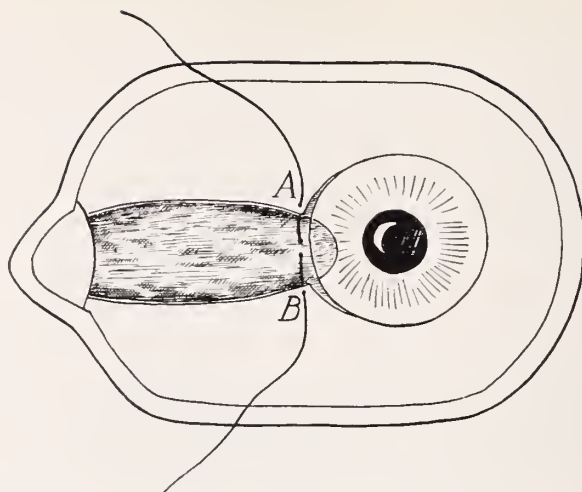


FIG. 3 Episcleral suture uniting cut edges of released limbus conjunctiva

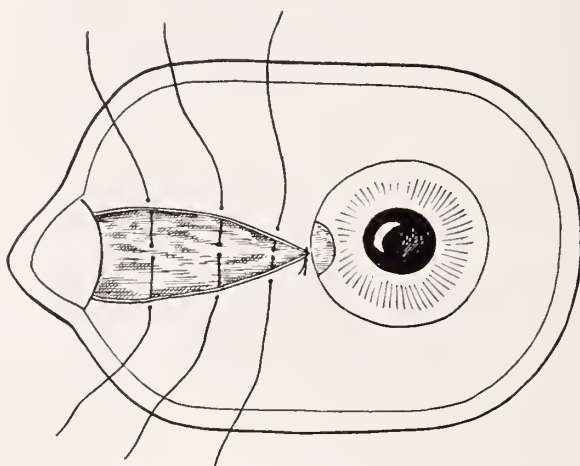


FIG. 4 Limbal suture tied and three conjunctival-episcleral sutures prepared

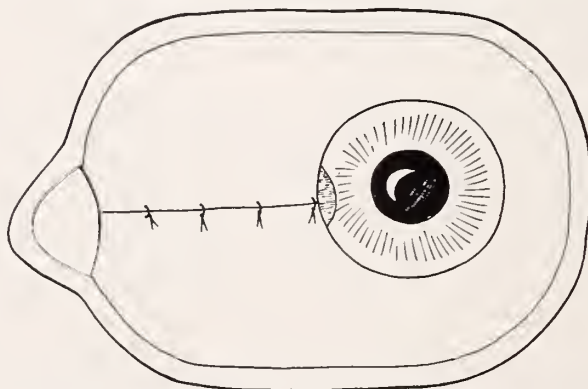


FIG. 5 Conjunctival and limbal sutures approximated

## COMMENT

The method of simple excision described has several obvious advantages. In excising conjunctival and subconjunctival tissue in one layer, special treatment of the subconjunctival or submucosal layer is not required. In most instances, sclera covered by a thin layer of episcleral tissue is exposed following removal of the bulk of the growth.

Further growth of remaining actively growing tissue is prevented by the virtual obliteration of the subconjunctival space, and by the restoration of normal limbus. There is very little post-operative reaction. The horizontal conjunctival wound heals promptly and no instance of gaping has been observed when the sutures are properly placed. The head of the pterygium is completely removed and the limbal area anatomically restored. The cosmetic appearance is uniformly excellent, and to date not a single instance of recurrence of the growth has been observed.

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## CLOSURE OF PHARYNGOSTOME BY DISTANT OPEN LINED FLAP\*

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Successful closure of large pharyngostomes following radical surgical intervention for removal of extensive carcinomatous lesions in the pharynx and larynx is a challenge and demands a constant search for improved methods. The literature offers a variety of procedures for plastic repair of pharyngostomes. Thus, Gluck and Soerensen (1,2) constructed a tube from a folding-door flap on one side of the pharyngeal opening. The raw surface was then covered with a sliding flap of skin from the other side of the neck. In a modification the raw area was covered with a Thiersch graft. Wessely (3) turned in flaps raised from the edges of the pharyngostome, and then covered the inner flaps with a double-pedicled sliding flap from the submental region. He also used an alternate method in which the same type of flap was advanced from the chest wall. Both of these methods resulted in further defects and were applicable to small stomata only. In addition, this technique required healthy surrounding tissues. Padgett (4) also utilized the turned in edges of the stoma but interposed a layer of ribbon muscles which, in turn, was covered with a sliding cross-lapping flap from the neck. Traina and Simmetta (5) used a flap from the submental region turned down like a trap-door over the stoma and covered the raw area with a free skin graft. In this method, there was the disadvantage of turning in hair-bearing skin and thereby creating another deformity. Martin (6) effected closure of smaller pharyngostomes by raising a flap of skin and subcutaneous tissues from one side of the opening and turning this flap around with advancement of a similar flap from the opposite side so as to provide an epithelial lining for the anterior wall of the pharynx. In larger openings, tube pedicle grafts raised from the anterior chest wall of lateral sides of the neck were employed. Ivanissevich and Ferrari (7) raised a panhandle tubed-flap from the subclavicular region, rotated the distal end with the skin surface turned into the pharynx and covered the raw surface with a sliding flap from the neck. An alternate technique employed the distal part of the tube to cover the stoma partially and then rotated the rest of the tube pedicle to close the remaining defect. Diaz (8) used a flap from the vestibule of the larynx to create the pharyngeal tube. This method required sufficient healthy tissue in the larynx. Wookey (9) described a technique to be employed following the removal of the entire hypopharynx. A flap from the neck was laid across the prevertebral fascia. A tube was then created by raising the edges, and the raw surfaces were covered with a sliding flap from the neck.

It is our aim to report and illustrate a method of closing a large pharyngostome, utilizing surgical principles observed by us at Plastic Surgery Centers of the Medical Department of the U. S. Army during World War II for the repair of traumatic defects in other parts of the body. It is the open flap technique

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which affords a more direct approach than the tube flap in the repair of large defects.

The closure of a large defect in the case to be reported was accomplished by the use of a delayed, distant, open, lined flap taken from the chest wall. The flap was begun in the subclavicular region and then was extended out to the axilla in order to utilize glabrous skin for the pharyngeal aspect. The distal inferior surface was lined with a split-thickness graft in order to provide an external epithelial surface for the flap when it was swung upwards to close the pharyngostome. In this way torsion of the pedicle was avoided.

#### CASE REPORT

*History.* D. F. (No. 568833), a man aged 52 years, entered the Otolaryngological Service of The Mount Sinai Hospital on November 21, 1946 because of serious respiratory obstruction and difficulty in swallowing of several days' duration. He had noted persistent hoarseness for three months.

*Examination:* There was infiltration of the right aryepiglottic fold, arytenoid and pyriform fossa. The arytenoid was fixed. The glottic chink was narrowed to 2 mm. There were no palpable cervical lymph nodes. Roentgenogram of the chest showed no significant findings. A tracheostomy was performed the day following admission. Biopsy from the right pyriform fossa, taken on the day of admission, was reported "squamous cell carcinoma".

*Course:* The patient was referred to the Radiotherapy Department where irradiation was administered from November 26, 1946 to December 31, 1946. A course of 4000 r in air was given to the larynx from each side of the neck. The patient was then observed in the Follow-Up Clinic for five months, during which time no disease was noted. One month later, about six months following completion of radiotherapy, edema of the right pyriform fossa, arytenoid and pharyngeal wall reappeared and progressed rapidly. This was accompanied by recurrence of dysphagia, loss of weight and appearance of streaks of blood in the tracheal secretion.

He was readmitted to the Otolaryngological Service on August 15, 1947. Direct pharyngoscopy, at that time, showed the presence of an irregular mass involving the right aryepiglottic fold and extending across the pyriform fossa to the lateral wall of the hypopharynx at the level of the upper portion of the arytenoid. Biopsy of the pyriform fossa again disclosed evidence of squamous cell carcinoma.

The patient was given penicillin because of the fullness and tenderness in the submandibular and anterior cervical regions and slight fever. Roentgenogram of the chest revealed focal atelectasis in the middle third of the right lung. On bronchoscopy, a moderate amount of thick secretion reappeared from the right upper and middle lobe bronchi. Repeated bronchoscopic aspirations and instillations of penicillin solution directly into the affected bronchi were performed for ten days until the infection subsided.

*Operation:* Total laryngectomy and hypopharyngectomy were performed on September 19, 1947. The neoplasm was found to have extended from the right pyriform fossa down the posterolateral wall of the pharynx to the cricopharyngeus, and mesially through the ala of the thyroid cartilage. It was intimately adherent to the right superior thyroid and superior laryngeal vessels as well as to the carotid sheath. The tracheal stump was brought out through a new stoma and the bridge of tissue above it was reinforced by overlapping the cut ends of the sternohyoid muscles.

The postoperative course was satisfactory but was marred by a severe hemorrhage due to inadvertent removal of the ligature on the right superior thyroid artery. This required the ligation of the external carotid artery. It was necessary to wait for a period of four months until the patient's general condition had improved sufficiently to permit plastic closure of the pharyngostome.

Until the pharyngostome was closed, the patient fed himself by inserting a rubber tube into the esophagus before each meal, which he easily accomplished in front of a mirror.

*Plastic Repair:* The pharyngostome measured 9 x 6 cm. (fig. 1) when the flap was originally prepared, and ultimately contracted to 4 cm. in width. To provide



FIG. 1. Pharyngostome before plastic repair

an excess of tissue, a rectangular flap measuring 24 cm. long and 10 cm. wide was marked out on the left anterior chest wall. The flap was begun in the sub-clavicular region to include the upper anterior intercostal arteries and was extended out into the axilla to secure smooth hairless skin at its termination for turning in to the pharynx. Two parallel incisions through skin and subcutaneous tissue were made (fig. 2). The flap was undermined and resutured to its bed with #000 chromic catgut for the superficial fascia and fine black silk sutures for the skin. The central portion of the flap where it crossed the anterior pectoral fold

became necrotic at its superior margin. To ensure viability the flap was delayed a second time. The distal third of the flap was then undermined and its under surface was lined with a free split-thickness graft from the thigh. The bed of the flap was similarly covered. A strip of vaseline gauze was brought through the pocket to separate the skin grafts (fig. 3).

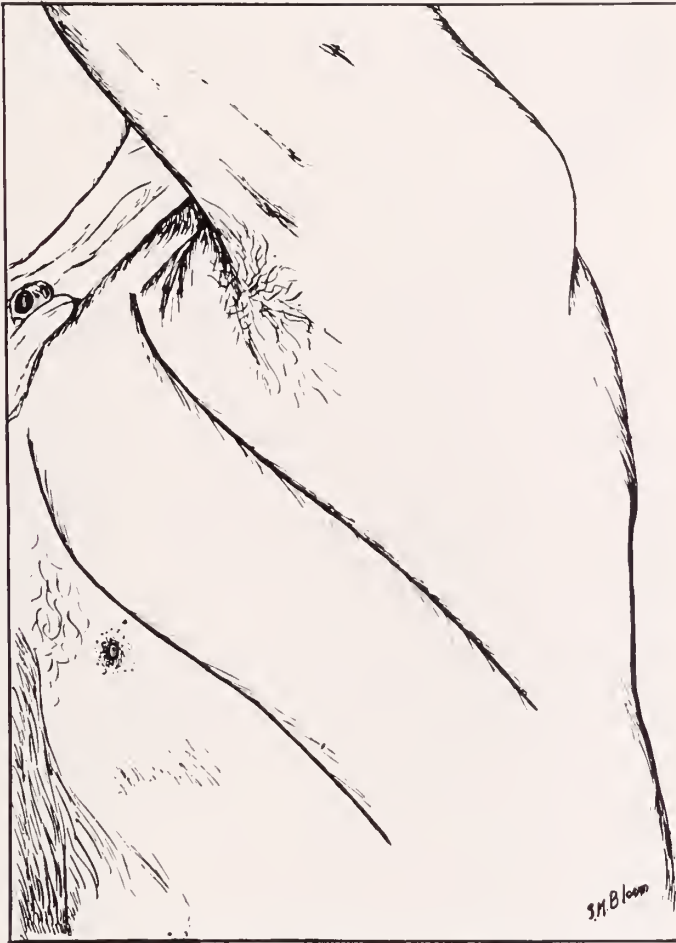


FIG. 2. Outline of flap on chest wall

Intermittent pressure was applied by an intestinal clamp to the distal border of the flap over a period of nine days to stimulate circulation at its proximal end. The distal border of the flap was severed and the flap was raised from its bed. The bed of the flap was covered partially by undermining the edges of the defect. The edges of the pharyngostome were undermined for about 0.5 cm. from the margins to serve as a bed for the borders of the flap. The distal lined end of the flap was sutured to three sides of the pharyngostome in two layers (fig. 4). Suture of the inferior angle was delayed in order not to compromise the circula-



tion of the pedicle. On the pharyngeal aspect, interrupted #000 chromic catgut sutures were used to approximate the mucous membrane to the skin surface of the flap in a manner which brought the knots into the hypopharyngeal space. On the external aspect, the skin-grafted surface of the flap was approximated to the skin of the edges of the pharyngostome with Dermalon. A plaster cast was applied



FIG. 3. Delayed flap showing distal portion lined with split-thickness graft

to immobilize the head and neck. The attachment of the flap healed well except for a slight separation at the right border which was easily repaired.

At this stage, the progress of the patient was interrupted by an episode of mild fever, productive cough and vomiting. A portable roentgenogram of the chest revealed a metastatic tumor in the midportion of the right lung posteriorly at the level of the 6th and 7th ribs. An excision of the apical segment of the right lower lobe containing the metastatic carcinoma was performed by Dr. Arthur S.

W. Touroff. A hilar lymph node removed at the time also showed metastasis. The wound healed in six days.

After a period of ten days of intermittent pressure at the inferior border of the lined portion of the flap, the final step in the plastic procedure was accomplished. The pedicle was severed and returned to its bed on the chest wall. The

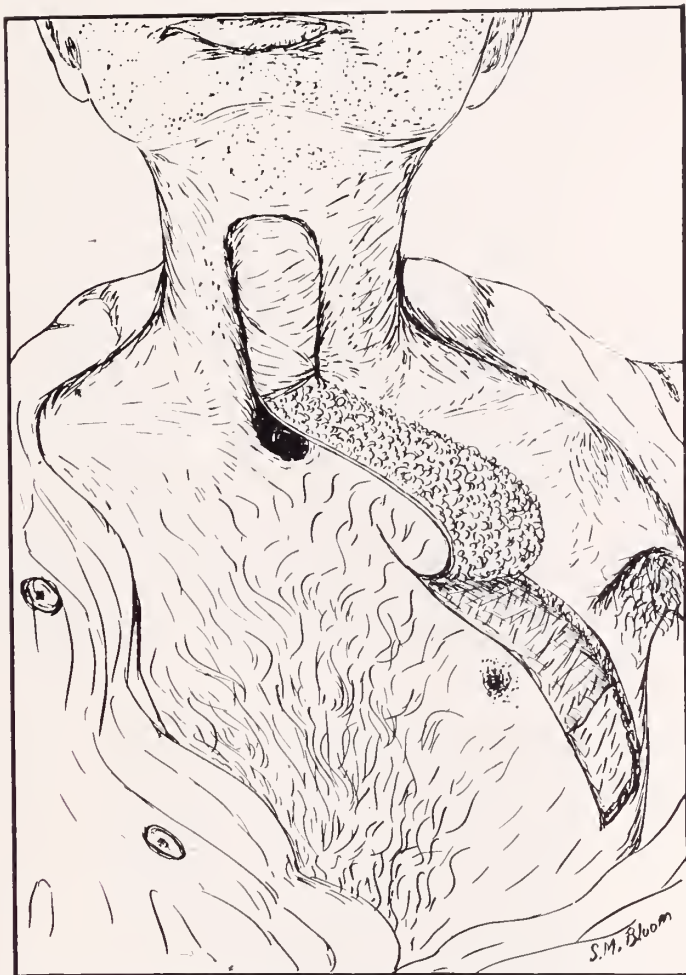


FIG. 4. Flap swung to neck and sutured to pharyngostome except for inferior angle

edges of the remaining defect at the inferior angle of the pharyngostome were freshened and sutured in pharyngeal and dermal layers. A slight separation of the suture line on the right side developed and this finally healed after secondary repair (figs. 5A and B). After the plastic closure was completed, the patient was able to swallow well. He gained weight and was discharged from the hospital on March 28th, 1949.

Four months after the secondary repair a swelling appeared in the left supra-

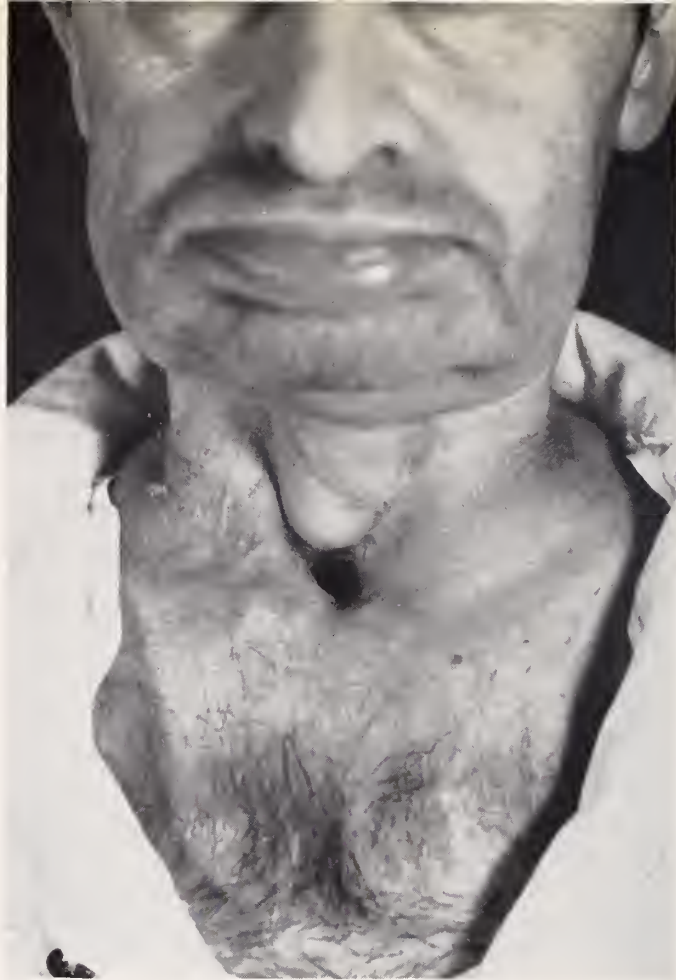


FIG. 5A. Repaired pharyngostome



FIG. 5B. Repaired pharyngostome

clavicular region. A second course of x-ray therapy of 4550 r was given to this area from July 7th to August 9th. Subsequently, the patient's general condition deteriorated and difficulty in swallowing appeared due to lower esophageal obstruction. The patient was admitted to Montefiore Hospital on November 2, 1949 where a gastrostomy was performed. He died on December 7, 1949. Post-mortem examination revealed extensive metastases to the lymph nodes of the mediastinum and the left first rib. The mediastinal masses had compressed the trachea and obstructed the esophagus. There was no local recurrence in the neck, however, and the plastic closure was in good condition.

#### SUMMARY

A method of closing a large pharyngostome by swinging a delayed, open, full-thickness flap from the anterior chest wall has been described. By lining the distal third of the flap, sufficient tissue was brought directly to the defect without torsion. The distal portion of the flap was obtained from the axilla to avoid hair-bearing skin on the anterior chest. An efficiently functioning pharynx thus was constructed. In retrospect, it seems that it would have been better to fashion the flap from the tissues of the anterior chest in order to obviate the partial loss of tissue which resulted from compromising the circulation at the level of the anterior pectoral fold.

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# SURGERY FOR DEAFNESS IN CONGENITAL ATRESIA OF THE EXTERNAL AUDITORY CANAL

WITH REPORT OF A CASE

SAMUEL ROSEN, M.D.

Congenital absence of the external auditory meatus has a reported incidence of one in two thousand aural cases. One out of every six such abnormalities is bilateral. The deafness is profound. For many years attempts to improve the hearing by all sorts of surgical procedures (radical and modified radical mastoidectomy with and without skin grafting) ended in failure. All the plastic operations to create a new auditory canal without surgery on the bone were doomed to failure. Misunderstanding of the embryonal development of congenital atresia accounted for the prevailing pessimism among otologic surgeons.

Kisselbach in 1883 is credited with the first surgical attack on this anomaly. Dean and Gittins (1) in 1917 reported the best surgical results in improved hearing. Beck (2) in 1925 emphasized the psychological aspects of the problem and reported improved relations of the patient after an operation had restored an external auditory canal even though the hearing was not improved.

Fraser (3) (1931) and Richards (4) (1933) stressed the embryological defect of the external and middle ear structures which produces this malformation and deafness. They pointed out that embryologically the cochlea and labyrinth develop much earlier and from a different anlage than the middle ear, ossicles, or external ear. Congenital defects of the inner ear, therefore, usually occur without associated defects of the middle ear and external ear. Congenital defects of the external and middle ear structures usually occur without associated defects of the internal ear.

Fraser states, "In a typical case the auricle is malformed in varying degrees or almost absent, the external meatus is occluded by bone, the malleus is small or absent while the incus is large but misshapen, the tympanum is narrowed in breadth or height and the window niches are occluded by connective tissue . . . the facial nerve is usually small and may cross the tympanum uncovered by bone.". The above may occur in varying combinations with facial paralysis or facial asymmetry. Fusion of the malleus and incus is common.

Although the operation to correct the atresia is most urgent for patients with bilateral deformity with impaired hearing and speech defect, Hume and Owens (5) in 1935 advocated the operation in unilateral cases as resulting in improved hearing and great psychological benefit. There had been wide disapproval of operating unilateral cases except if such an atresic ear became infected. In approving surgery in unilateral cases, Rosenberger (6) (1949) states, "In this era of emphasis on hearing conservation, it would seem a discordant philosophy that offers help to a child with unilateral conduction deafness of inflammatory origin but denies aid to another child with a similar defect of congenital origin.". Rosenberger's evaluation stimulated the surgery in the case here reported. The

greater the total combined hearing in both ears, the better can it withstand the hazards that assail this sense throughout life.

In unilateral cases the speech and hearing may appear normal although the hearing in the atresic ear may be greatly reduced. The atresia produces a typical severe conduction type of deafness. In 1947 Pattee (7) introduced a new viewpoint in evaluating these cases. He was impressed by the similarity of audiograms in clinical otosclerosis and congenital atresia. He postulated that the hearing defect in congenital atresia resulted from stapes immobility due to the fused immobile malleus and incus. Similarly in clinical otosclerosis the hearing defect results from stapes immobility due to fusion and fixation of the stapes in the oval window. In many cases, as in mine, this finding of fused malleus and incus would suggest the validity of Pattee's theory.

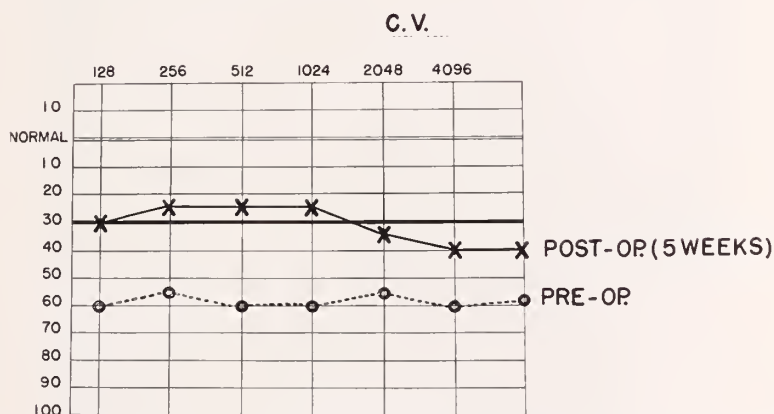


FIG. 1. Dotted lines (circles) show the preoperative hearing far below the useful level. Solid lines (crosses) show the useful hearing level five weeks after the operation.

#### REPORT OF A CASE

C. V., a girl of eight brought from Colombia, South America, was seen April 19, 1950. Her left auricle, external auditory canal, and the hearing in this ear were all normal. The right auricle was considerably smaller than the left, obviously deformed, and the external auditory canal was absent, being replaced by bone. Audiometric and tuning fork tests revealed markedly impaired hearing far below the level of usefulness (fig. 1). The Weber was referred to the affected ear with excellent bone conduction typical of a conduction deafness. In January-February, 1950, the child suffered a severe bilateral acute middle ear infection which caused temporary but profound deafness in both ears. The parents for the first time became aware of the potential dangers to total hearing from infection in the normal ear, as well as the difficulties involved in treating infection in the congenitally atresic ear. The parents therefore approved of surgery which could offer a wide open external auditory canal and possibly restored hearing. Roentgenograms revealed pneumatized mastoids bilaterally.

On April 24, 1950, under general anaesthesia, the endaural surgical approach was employed. None of the usual guiding landmarks on the surface of the mastoid were present, nor was anything seen to suggest the location of an external auditory canal. The dissection was carefully followed until the mastoid antrum was found and enlarged. Further exploration brought the horizontal semicircular canal into view. The facial nerve could not be positively identified. As the tympanic cavity was enlarged the malleus and incus came into

view. They were found to be fused together as one and were delivered with difficulty (fig. 2). The stapes on palpation was freely moveable. The tendon of the tensor tympani muscle and



FIG. 2. Upper photograph shows normal malleus and incus removed from a cadaver. Lower photograph shows abnormally fused and distorted malleus and incus removed at operation.

the chorda tympani nerve could not be seen. The absent drum membrane was replaced by thick solid bone.

The mastoid was partially exenterated and a split-thickness skin graft cut from the thigh was draped over a moistened cotton stent to fit the mastoid cavity and tympanum.

Healing was satisfactory. The result of this surgery provided a wide bony canal as far inward as the tympanum and the hearing has improved 20-35 decibels in all frequencies to the useful level (figs. 1 & 3).



FIG. 3. Ear canal established by the endaural route

#### SUMMARY

1. Congenital atresia of the external auditory canal represents partial agenesis of the entire ear mechanism, the cochlea and labyrinth being spared.

2. Surgery for bilateral congenital atresia is mandatory.

3. Surgery for unilateral congenital atresia appears indicated to salvage hearing and improve psychological relations of the patient.

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## WHAT IS JUSTIFIABLE SURGICALLY IN MÉNIÈRE'S DISEASE?

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It is not within the scope of this brief communication to attempt an adequate survey of the voluminous literature dealing with the surgical treatment of Ménière's Disease. Rather, it is my purpose to discuss certain aspects of Ménière's Disease and from this discussion and from our present knowledge determine what is justifiable to do in the surgical treatment of Ménière's Disease.

A surgical approach for the relief of symptoms resulting from Ménière's Disease was described by Knapp (1) in 1871, who postulated increased intralabyrinthine pressure as the etiologic factor. In 1938, Hallpike and Cairns (2) histologically demonstrated gross distention of the endolymphatic system and degenerative changes in the sensory elements in the labyrinth and were the first to provide proof of what had been theorized by Knapp. They stated that once the dilatation of the endolymphatic system had attained its maximal degree, then the fluid system of the membranous labyrinth, from being insensitive, becomes at once extremely sensitive in its pressure response to a given volume increase of the endolymph. In this fashion it is possible to explain the attacks as being due to rapidly initiated bouts of asphyxia of the labyrinthine end organs brought about by extremely rapid rises of fluid pressure in response to very small volume increases in the endolymph. The histologic findings of Hallpike and Cairns have been corroborated by Lindsay (3), Altman and Fowler (4) and others, and have lent authority to the concept that Ménière's Disease is primarily a disturbance of the vestibular end organ and not a disease of the vestibular nerve. Acceptance of this concept may explain the renewed interest in the medical treatment of this disease and in the utilization of procedures aimed at the destruction of the vestibular end organ and perhaps explains some of the lessening enthusiasm for eighth nerve section.

As stated by Lathrop (5) the surgical management of Ménière's Disease has received much attention from neurosurgeons and otologists during the past decade. As a result there now are a number of operations which may be employed to alleviate the symptoms of Ménière's Disease, after conservative medical care has proven ineffective. The surgical techniques aimed at eradication of the disturbing and disabling symptoms of Ménière's Disease by destruction of the end organ may be divided into three groups. The first, employs the principle of injecting alcohol into the peri-labyrinthine space either through the foot plate of the stapes (Wright (6)) or through a fistula in the external semi-circular canal (Mallison and others (7)) thus causing destruction of the vestibular end organ. The second endeavors to accomplish the same end result by avulsion of the membranous semi-circular canal by way of a fenestra made in the horizontal semi-circular canal, as practiced by Cawthorne (8), Kenneth Day (9), advocates

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and uses an electro-coagulating current to the exposed membranous labyrinth in order to destroy the vestibular end organ. Lempert (10) accomplished what he termed atraumatic and aseptic degeneration of the entire endolymphatic system by his transtympanic operation, removing the stapes and destroying the round window membrane. In his opinion any technic expected to relieve the symptoms must supply a reasonable basis for the belief that the entire endolymphatic labyrinth will degenerate and thus render occurrence of endolymphatic hydrops impossible.

Approaches aimed at elimination of the endolymphatic hydrops have been reported by Portmann (11) (endolymphatic sac operation) and Garnet Passe (12) (stellate ganglion operation). These procedures theoretically attempt relief of the hydrops rather than destruction of the end organ. Further experience and study must be awaited to properly evaluate the utility of these latter procedures. Lastly, are the techniques described and popularized by the neurosurgeons. Dandy (13) aimed at disrupting the pathway between the vestibular end-organs and the central vestibular nuclei. The procedure described by Dandy was modified and theoretically improved by Mac Kenzie (14) who attempted to section only the vestibular portion of the eighth nerve, and thus preserve the residual hearing present preoperatively. Neurosurgeons consider this procedure the one of choice for the surgical treatment of Ménière's Disease. Brain (15) advocated this procedure in resistant and incapacitating vertigo and claimed it was practically free of risk and attendant with excellent results. Putnam (16) stated that this procedure was the accepted one in the United States, but added that it was not always as easy, rapid and safe as some accounts would lead one to believe. Putnam, in turn, advocated a sub-temporal decompression with destruction of the superior semi-circular canal. He felt this approach entailed less danger of producing deafness than the previously mentioned procedure.

After analysis of 36 cases of eighth nerve section at the Mayo Clinic, Williams (17) stated that in the instances in which hearing was preserved, the vertigo remained and in those instances in which the vertigo was relieved, the hearing was completely lost. As stated by Lathrop, the real intrinsic value of any surgical procedure can be ascertained only after it has been employed in a comparatively large group of representative cases whose postoperative follow-up is sufficiently long to determine whether or not the desired objective was achieved.

I have always been guided by certain specific considerations in deciding which of the cases of Ménière's Disease should be treated surgically, and, it is here I believe, that differences of opinion may arise. I do not believe cases of Ménière's Disease with good serviceable hearing are ever justifiable candidates for surgery. These are the cases in which study and investigation from the modern metabolic, allergic and endocrinologic view-point should be carried out. Vertigo is the most distressing symptom of this condition. It may be severe, often of unpredictable frequency and duration and result in complete incapacitation. It may eventuate in what has been termed chronic vertigo, confine patients to the

home making them afraid to venture out unaccompanied. And, when it occurs in the wage earner of the family, making it impossible for him to be continuously and gainfully employed, it poses not only a medical problem but an economic one as well. If in addition, severe nerve deafness has resulted, so pronounced that even with the use of a modern hearing aid, serviceable hearing cannot be obtained, and if the hearing disability is unilateral, with associated annoying tinnitus, there can be little valid cause for objection to surgery. In such an instance as described above, I am not deterred by the possibility of involvement of the good ear. This possibility exists whether or not the patient is operated upon. Cawthorne felt no useful object could be served by trying to preserve a distorted remnant of hearing unless there was good reason to suppose that both ears were actively involved.

The two cases are herein reported in order to demonstrate when I believe surgery is indicated. The type of operation performed was selected because of its ease of performance and because there is present ample data to indicate its efficacy in destroying the vestibular end organ, with relief of the vertigo. Whether or not this procedure is successful in making impossible a recurrence of endolymphatic hydrops still remains to be proven.

#### CASE REPORTS

*Case 1. History.* J. D. (#600544) aged 58 years, was admitted to the ENT Service complaining of progressive hearing impairment in the right ear, dizziness, nausea and vomiting of 9 years duration. These attacks occurred about once a month, lasted 4-5 hours and were relieved only by rest and sleep. There also has been associated hissing (high pitched) tinnitus during this time. During the vertiginous attack, the tinnitus became accentuated. The patient's distressing dizziness had increased in severity and frequency during the past nine years and at the time of admission occurred almost daily.

The patient had consulted many physicians and had been treated with all the known, accepted, medical methods without relief. There was no family history of deafness, no paracusis willisi. The remainder of his past history was essentially negative.

*Examination.* The patient, a white man, was not acutely ill. The pupils reacted promptly to light and accommodation. The vessels of the oculi fundi showed increased light reflex. There were no arterial or venous changes. The optic discs were normal. The heart was not enlarged. The sounds were of good quality A2 > P2. The blood pressure was 120 systolic and 72 diastolic and there was no evidence of arteriosclerosis. Both middle ears were normal; all landmarks were present.

*Laboratory Data.* The blood Wasserman reaction, the urine and the blood studies were negative. Blood chemistry findings indicated total protein was 74 mgs. per 100 cc. X-rays of the skull showed some slight widening of the sella turcica; its depth, however, was not abnormal. The pineal body was not displaced. The internal auditory meati were normal. Electrocardiogram revealed slight changes indicative of involvement of the myocardium. There were no clinical evidences of myocardial insufficiency. Lumbar puncture revealed clear fluid, normal pressure, no abnormal findings. Total protein was 58 mgs. per 100 cc. Caloric tests revealed no spontaneous nystagmus or past-pointing. Stimulating the right horizontal and vertical semi-circular canals, using 100 cc. of feed water yielded little or no response for nystagmus, past-pointing or vertigo, whereas, stimulation of the left horizontal and vertical semi-circular canals using 20 cc. of cold water, yielded prompt normal responses for nystagmus, past-pointing, vertigo and falling. Audiometric (fig. 1) and tuning fork tests indicated the presence of a perceptive mechanism type of hearing impairment on the right side of severe degree, with excellent hearing on the left side.



*Consultations.* Ophthalmologist, Neurologist, and Internist reported no significant findings and no contraindication to surgery. Psychiatric investigation revealed no overt evidence of psychopathology and it was felt that the attacks of vertigo did not seem to be related to any episodes of emotional stress.

*Course.* While being studied, the patient continued to have almost daily attacks of dizziness. During this time, nystagmus was noted horizontally directed to the right, with a rotatory component noted on upward gaze.

*Operation.* Endaural mastoidectomy was performed with exposure of the surgical dome of the vestibule. A large fenestra was then made exposing the membranous labyrinth. The membranous labyrinth was avulsed and the peri-lymph space of the vestibule allowed to fill up with blood. No attempt was made to cover the fenestra.

The cavity was packed loosely with paracine mesh gauze. The patient was given 300,000 units of erythiicillin daily.

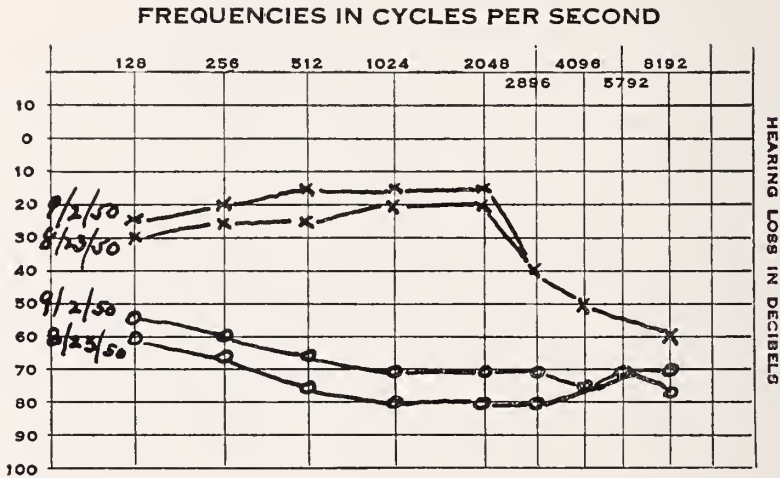


FIG. 1. Audiogram revealing hearing for air conducted sound taken 8/23/49 and 9/2/49, of the right (o) and left (x) ears. The variability in hearing in Ménière's Disease is well known clinically. There is also a known and oftentimes marked variation in the responses which occur with caloric testing in Ménière's Disease.

*Post-operative Course.* The temperature was normal. On the 2nd post-operative day the patient had very little vertigo, except following sudden change in position. There was present marked nystagmus to the left side. The patient was eating and had no nausea or vomiting. On the 6th post-operative day the patient sat up all day and walked about the ward, though he was slightly unsteady. The patient was discharged from the hospital on the 10th post-operative day, free of vertigo but with slight tinnitus still present.

*Follow-up.* The patient was followed carefully at short intervals in our Out-patient Department and still is under observation. He has been free of all dizziness, is able to drive an automobile and is very pleased with his present status. The tinnitus is still present, but apparently does not disturb the patient very much.

*Comment.* I would like to point out that absent or markedly diminished caloric responses does not mean a totally dead labyrinth. It only indicates that the thermic stimulus, which ultimately reaches the inner ear at that time, is not sufficiently strong to cause noticeable responses for nystagmus, vertigo and past-pointing. Despite this, it is possible that this labyrinth may be the site from which disabling attacks periodically are initiated.

This patient is apparently well and happy thus far and the result is dramatic. However, it should be pointed out, that Ménière's Disease in its clinical course is characterized by

spontaneous remissions, often entirely independent of therapy, which vary from short periods of time, to long intervals. Only after prolonged observation can the end result of surgery be accurately assessed.

*Case 2. History.* (#601338) J. R., a 52 year old man, was admitted in September, 1949, complaining of severe incapacitating dizziness which prevented him from working for months. He is married and the sole support of his family. For many years, the patient suffered from recurrent disabling attacks of dizziness, severe tinnitus and marked deafness in the right ear. The remainder of his history was not significant.

*Examination.* The patient was a stocky, stolid, Puerto Rican man with inconstant nystagmus to the left on lateral gaze. The ear drums were normal; all the landmarks were present. Tuning fork tests and audiometric study (fig. 2) revealed an advanced perceptive mechanism type of hearing impairment on the right side, the loss varying between 60-80 decibels for the critical speech frequencies. X-rays of the mastoids, blood Wasserman re-

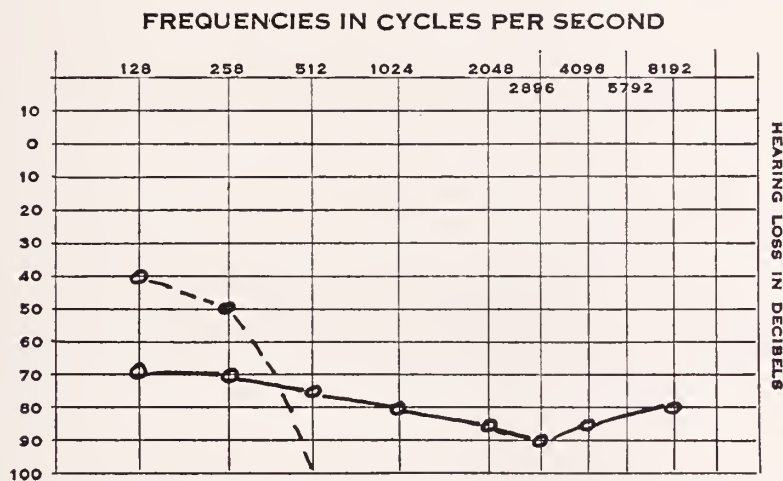


FIG. 2. Audiogram revealing hearing for air conducted sound taken 9/13/49 in the involved right ear using masking noise in the relatively good hearing left ear. The dotted line indicates bone conduction. This audiogram reveals advanced nerve deafness.

action, blood studies, urine analysis were all negative. A complete neurologic study was entirely normal. Caloric test revealed markedly diminished responses for nystagmus, past-pointing. There was no vertigo and no falling on stimulating the *right* horizontal and vertical semi-circular canals. The responses were somewhat more marked on the left side for nystagmus and past-pointing. There was little vertigo or falling.

*Operation.* Endaural mastoidectomy was performed, exposing the surgical dome of the vestibule. A large fenestra was made in the surgical dome exposing the membranous labyrinth. The membranous labyrinth was avulsed and the peri-lymph space of the vestibule permitted to fill with blood. The fenestra was not covered with skin flap. The patient was put on penicillin therapy, 300,000 units daily.

*Course.* The postoperative course was characterized by extreme vertigo and unsteadiness. For a while the patient was afraid to get out of bed because of the unsteadiness. The dizziness and tinnitus gradually diminished, and on the 18th post-operative day the patient was discharged from the hospital.

*Follow-up.* The patient has been seen at frequent intervals. The last time was May 1950, at a monthly clinical conference. He was absolutely free of dizziness. The tinnitus had subsided very noticeably. The patient was grateful and happy to be back at gainful work.

*Comment.* According to available statistics, the incidence of bilateral involvement in Ménière's Disease varies from 10% (Cawthorne) to 28% (Wright), which is cause for concern in either instance. This is one of the factors which requires careful study and integration into the overall picture in determining in which cases surgery is justifiable in Ménière's Disease.

Day (18), in his earlier cases was hopeful of preserving hearing, but has since stated that as a general rule he could not report such good results. Some of the patients previously reported by him as having had useful hearing in the operated ear, developed gradual deterioration, eventuating in more or less complete deafness.

According to the experimental work of Schall and Rambo (19) where optimal current was used in electro-coagulation, the damage to the membranous labyrinth of the vestibule and semi-circular canals was complete and predictable, the damage to the cochlea, unpredictable. Retention of serviceable hearing following this operation was believed improbable. Lindsay (20), in commenting on conclusions drawn from the study of sections of the cochlea in experimental animals that had their membranous labyrinths electro-coagulated, said, "It should be realized that interpretations which can be made from the histologic picture alone are limited. Any extensive histologic deviation from the normal is probably incompatible with useful function. However, even in the presence of a fairly normal histologic picture, it cannot be assumed that function is correspondingly good or even present."

I do not believe that avulsion of the membranous labyrinth as recommended by Cawthorne, after which he noted profound deafness in all his cases, is anti-thetic to the observation that has been made by some, that injury to the membranous labyrinth during fenestration operation is not always associated with profound hearing loss. Very significant, I believe, is the fact that in Cawthorne's procedure, the labyrinth opening is not covered with a skin flap as is the case in the fenestration operation. Williams (17) after avulsing the membranous labyrinth packs the fenestra with bone dust and bone chips in order to obtain an early closure stating, "Considering the pathologic basis for the physiological alteration which is present in Ménière's Disease, it would be unreasonable to expect preservation of hearing after electro-coagulation of the membranous labyrinth." I am in complete accord with the viewpoint clearly expressed by Williams.

As stated by Hallpike and Cairns (2) "With regard to tinnitus, it cannot be said that the anatomical changes found in our cases provide any new evidence which bears either upon its mode of origin or upon the well known but puzzling fact that following section of the eighth nerve cessation of the tinnitus occurs in only a proportion of the cases although relief from the vestibular symptoms is almost the unvariable rule." It is difficult to explain this unless one assumes that the tinnitus is of cochlear origin in these instances. Day (16) noted that tinnitus remained a prominent symptom in those cases in his series in which the hearing was preserved, and that it was entirely eliminated or markedly diminished in intensity when the hearing was entirely lost. As a result, there is some question

in Day's mind as to the utility of trying to preserve the hearing in unilateral cases of labyrinthine hydrops. Despite the fact that there often is complete deafness in the ear post-operatively, many patients insist they hear better than before the operation because of the elimination of the low-pitched roaring tinnitus which previously existed. The high-pitched tinnitus often is unchanged. It is likely that the hearing seems better because there is no longer present the disturbing, masking effect of the tinnitus on the uninvolved, better hearing ear. I believe it wise to offer a guarded prognosis concerning the ultimate fate of the tinnitus after surgery in Ménière's Disease.

#### CONCLUSIONS

The present concept of Ménière's Disease now has an accepted, firm pathologic basis, namely, endolymphatic hydrops. This was first demonstrated histologically by Hallpike and Cairns, and has since been substantiated by numerous other reliable observers.

Vertigo is the most distressing symptom of Ménière's Disease and when it occurs in the mainstay of the family, making it impossible for him to be continuously and gainfully employed, it poses an economic as well as a medical problem. If in addition, the involvement is unilateral, and the nerve deafness present is of such degree that even with a modern hearing aid, serviceable hearing is not possible of attainment, then I believe there can be little valid reason for objection to surgery. In Ménière's Disease, when the hearing in the involved ear is good, there is little justification for surgery.

The tinnitus occurring in Ménière's Disease is often a distressing symptom. The prognosis concerning the fate of the tinnitus following surgical treatment of Ménière's Disease should be a guarded one.

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## RECONSTRUCTION OF THE LARYNX AND THE TRACHEA

(REPORT OF A CASE OF EXTENSIVE CICATRICIAL STENOSIS<sup>1</sup>)

MAX L. SOM, M.D.

Laryngotracheal stenosis due to cicatricial narrowing of the subglottic airway is a serious disability associated with a poor voice and often requiring a permanent tracheostomy. Such strictures are frequently the result of a hastily performed high tracheostomy, although in past years, intubation undoubtedly contributed to their formation. The cicatricial tissue usually forms as a result of the loss of the cartilagenous framework of the larynx. The cricoid, which is the only complete cartilagenous ring, is the one chiefly involved. The most common site for the occurrence of such fibrous tissue is the subglottic region where the lumen normally becomes markedly constricted. Other causes of stenosis are: penetrating wounds of the larynx, specific granulomatous infections, post-radiotherapy perichondritis, indwelling nasal feeding tube and surgical trauma.

Until recent years, the treatment of such stenosis has been limited either to frequent dilatation with triangular dilators or the insertion of rubber core molds in progressively increasing sizes. The outlook in cases of advanced stenosis has been practically hopeless.

The application of the principles of plastic surgery in the therapy of stenosis of the larynx and trachea offers a much brighter prognosis. The opening of the larynx and trachea with the excision of the scar tissue and the relining of the lumen with a skin graft will restore the airway in most instances.

Erich (1) placed a skin graft over a block of airfoam sponge rubber and had good results in maintaining a permanent lumen. Figi (2) was able to restore both airway and voice by employing a Vernonite, acrylic mold. Martin and Albright (3) made use of a stent mold without skin grafting, but synechia reformed and repeated dilatations were necessary. Cardwell (4) prepared an acrylic obturator of the entire larynx. The mold was kept in place by the lateral ventricular extension for six days, but was then ejected on cough. Robb (6) now suggests a lucite mold.

The case now to be reported is one of long standing, ossifying laryngotracheostenosis which presented many problems in re-establishing and maintaining an adequate airway, as well as in the final closure of the tracheostomy.

### CASE REPORT

History. L. H., a white male aged 28 years was first admitted to the Mount Sinai Hospital on June 16th, 1949. He spoke with a harsh, hoarse, esophageal voice which was hardly intelligible. He had been wearing a tracheotomy tube since thirteen months of age, at which time, in 1922, a tracheostomy had been performed for relief of laryngeal obstruction, due to diphtheria. In 1938, the tracheostomy was lowered at another hospital. He has had repeated, unsuccessful attempts at dilation of his laryngeal aperture and has had numerous

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consultations in quest of relief from the permanent tracheostomy. Mirror examination of the larynx revealed an infantile epiglottitis which was retracted to the right. The arytenoids were pulled anteriorly and a glottic chink of about  $1\frac{1}{2}$  mm. could be seen. Direct laryngoscopy showed the right arytenoid to be displaced forward and completely fixed. There was



FIG. 1. Anterior-posterior view showing normal diameter of trachea tapering to a conical point in the subglottic area.

a slight motility of the left vocal cord. The subglottic area was almost completely stenosed except for a small elliptical lumen, through which only the finest probe could be inserted. Retrograde tracheoscopy showed the subglottic lumen to be obliterated by a firm, stone-like mass, extending upward from the trachea.

An x-ray examination of the neck in the antero-posterior view showed a normal, tracheal lumen extending from the carina up to about the seventh cervical vertebra. At this point, it tapered to a conical point and could not be identified in the subglottic region (fig. 1). On lateral view, the subglottic and upper tracheal lumen was replaced by a dense, partially ossified mass, extending from the fifth to the seventh cervical vertebrae. The lumen could

be traced as a narrow column of air which was angulated and displaced posteriorly. The posterior body of the cricoid could be identified (fig. 2).

The patient was readmitted on July 11th, 1949 for reconstruction of the subglottic stenosis.



FIG. 2. Lateral view showing the loss of the tracheal lumen with replacement of the subglottic airway by calcified scar tissue.

#### SURGICAL PROCEDURE

*Step 1:* Under local anesthesia, the skin was incised vertically in midline from the thyroid notch down to the tracheostomy. The pre-tracheal muscles were retracted and the thyroid isthmus was doubly ligated. The thyroid cartilage appeared grossly normal but the cricothyroid membrane, the cricoid cartilage and the upper, three tracheal rings were replaced by dense scar tissue. The thyroid cartilage was divided in the midline and the alae were retracted, exposing



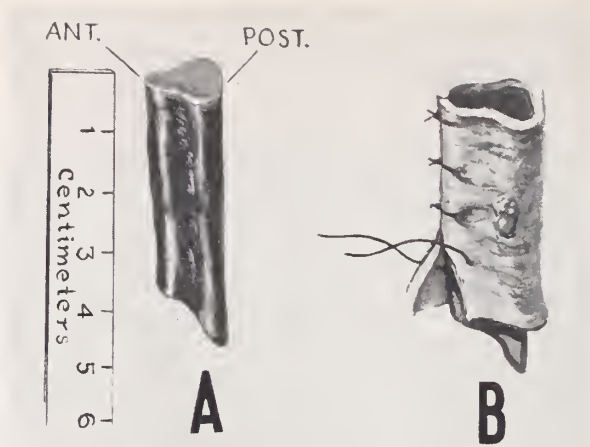


FIG. 3. Lateral view of the stent mold. The lower wedge-shaped extension (A) rested upon the tracheostomy tube. (B) The split thickness skin graft is wrapped around the mold and sutured. The raw surface faces externally and will be in contact with granulations on the tracheal wall.

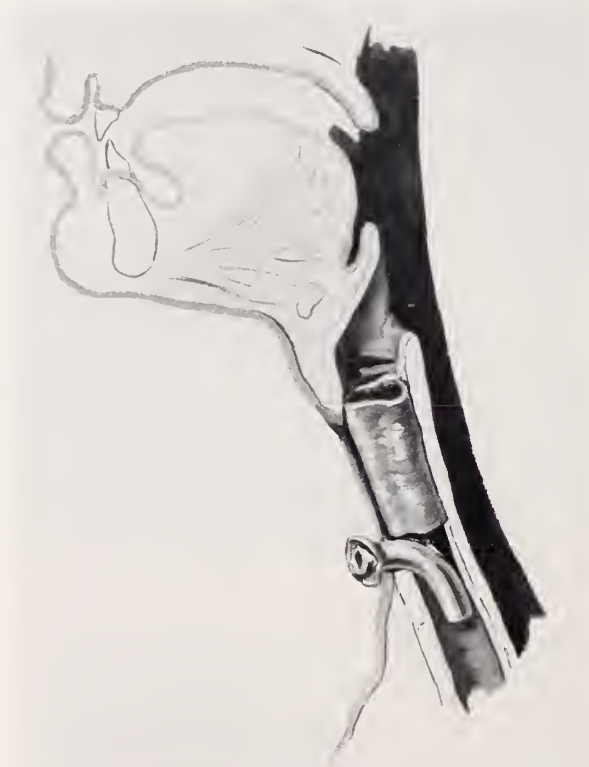


FIG. 4. The stent mold with the skin graft enveloping it is fixed in place, just below the vocal cords. The stent rests on the tracheostomy tube.

the interior of the larynx. The vocal cords were atrophic and almost completely fixed. The laryngeal ventricles appeared very shallow. Immediately subglottically on the posterior wall, a few, thin strands of scar tissue extended upward and were anchored to the arytenoid cartilage. About 1 cm. below the level of the glottis, the trachea became stenotic and the lumen narrowed to about 1 mm. A probe inserted into the lumen took an abrupt bend posteriorly. The remainder of the trachea, at this level was replaced by a dense, white, partially ossified



FIG. 5. The graft was taken and the entire subglottic and upper tracheal area is now epithelialized. A stent mold fits snugly into the tracheostomy but does not encroach on the lumen. The mold is fixed air-tight, by adhesive to the skin.

scar which included the collapsed anterior and lateral portions of the cricoid cartilage and upper, three tracheal rings. A small, groove director was inserted and the fibrotic mass was incised in the midline over it. The dense mass was now excised as completely as possible, a bone rongeur having to be employed to remove some of the calcified tissue. The lumen of the subglottic region and trachea was reestablished and reamed out until but a narrow rim of supporting cartilage remained laterally. The mucosa in the membranous, posterior wall was partially preserved. The denuded area at this time seemed avascular and was not thought to present a good bed for a skin graft. A stent mold, having the

contour of the newly created tracheal lumen was now prepared by permitting the heated stent to harden *in situ*. It was then fixed in place by approximating the perichondrium and strap muscles. The mold, which was about 4 cm. in length, rested on the tracheostomy tube below and was anchored to the skin by a silk retaining suture. Antibiotics were administered.

*Step 2:* One week later, July 19th, 1949, the wound was reopened and granulation tissue could be seen to line the lumen. A split thickness graft, about 5 cm. x 2 cm. was taken from the outer aspect of the thigh, and wrapped around the stent mold so that the skin surface was in contact with the mold and the raw area faced the tracheal wall (fig. 3). The long, free edges of the graft were fixed



FIG. 6. A right, lateral incision is made and the homologous cartilage graft is buried subcutaneously. The hidden cartilage is represented by diagonally, striped area.

over the mold by several sutures. The mold was now replaced into its original position in the trachea and the wound approximated by stay sutures. The tracheostomy tube was replaced (fig. 4).

*Step 3:* Ten days later, on July 29, 1949, the wound was reopened and the stent mold was temporarily removed. The skin graft was viable on all surfaces except posteriorly, where it overlapped the retained mucosa. The stent was replaced and the patient was discharged July 31st, 1949. For the next three months, the mold was kept in place and cleansed every few days through the intentionally, gaping wound. On October 21st, 1949, he was admitted to the hospital for re-examination of the trachea and evaluation of need for arytenoidectomy. With the stent removed, the lumen of the trachea conformed to that of the mold and was completely epithelized. The reconstructed airway was one

centimeter in cross section at its narrowest point and seemed thoroughly adequate. Attention was directed to the glottis which now was the site of the narrowest airway. The right cord remained fixed, but there seemed to be an increased motility of the left true cord so that the glottic space was about 3 mm.



FIG. 7. Photograph showing the right side of the tracheostomy to be more prominent, due to the buried cartilage graft. The skin incision is completely healed.

The tracheotomy tube was now removed and the opening in the trachea was covered airtight with adhesive tape. The patient was entirely comfortable breathing through his larynx for the first time in 28 years and showed no evidence of stridor on performing normal, physical exertion. His voice was tremendously improved and while still hoarse, was distinctly audible and understandable.



*Step 4:* A stent mold was now so fashioned that it fit snugly into the tracheostomy opening but did not encroach on the tracheal lumen. When fixed to the skin by adhesive, the mold occluded the tracheostomy allowing respiration to proceed through the natural, laryngeal passages. In addition, the mold prevented any possible, lateral collapse of the tracheal walls (fig. 5). It was decided not to perform an arytenoidectomy but to give the patient a trial period at work. The



FIG. 8. Closure of the tracheostomy. The skin and the buried cartilage graft will form the anterior wall of the trachea. The flap is swung to the left, using the intact skin, immediately to the right of the ostium, as a hinge.

patient got along well at work and was able to perform normal, physical activities without stridor.

*Step 5:* He was readmitted on January 2nd, 1950 for closure of tracheostomy. The opening in the trachea was about 4.5 cm. in length and 0.6-1 cm. in diameter. It was felt that a rigid, anterior wall at the site of closure would be most desirable, lest any sagging might compromise the tracheal airway. Accordingly, a piece of preserved, homologous cartilage with a thickness of about 2-3 mm. was selected for insertion into the anterior, tracheal wall. The dimensions of the cartilage graft were made slightly larger than the tracheostomy opening. Under

local anesthesia, a 5 cm. vertical incision was made parallel to the tracheostomy, at a distance of 1 cm. to the right. The skin was undermined, mesially, up to the very free edge of the stoma and prepared cartilage graft was now inserted, sub-



FIG. 9. The wound is completely closed. The patient is breathing through laryngeal airway with good voice.

cutaneously (fig. 6). The skin incision was closed with interrupted silk suture. The wound healed by primary union.

*Step 6:* The patient was readmitted after about an interval of one month. The skin to the right of the tracheostomy showed the firm prominence of the buried cartilage (fig. 7). Under local anesthesia, the closure of the tracheostomy was carried out by making use of cartilage insert in the anterior wall. The exact size and shape of the tracheostomy opening was carefully measured and out-

lined on the skin to the right of the ostium. The median margin of this outlined skin surface was to form the hinge on which the remainder of the skin flap would swing to span the tracheostomy. This medial border was hence not disturbed but a lateral, elliptical incision, as outlined (fig. 8), was made through the skin and through the underlying cartilage. It was found that the preserved cartilage was wider than necessary and not all was included in the flap. The cartilage graft was undermined, as far mesial as the free edge, care being taken not to expose the cartilage itself. An incision was then made on the left rim of the tracheostomy in its entire length and the edges were undermined. The skin flap with the hidden cartilage was swung to the left and sutured to the medial, fresh-cut skin surface with fine, chromic catgut. The skin on the left was undermined until it could be pulled over the midline and sutured to the right, closing the tracheostomy in two layers. The wound healed following this procedure (fig. 9), and for the past six months, the patient continued to perform normal, physical activities without difficulty. His voice is markedly improved.

#### SUMMARY

Reconstruction of the larynx and trachea in a case of cicatricial stenosis of twenty-seven years duration is reported. Complete excision of the calcified scar in the subglottic region, with re-establishment of the lumen was immediately followed by insertion of a stent mold. The raw surface was then relined with a split thickness graft which was fixed in place by the mold. The tendency toward contracture of the newly-formed lumen was overcome by prolonged use of the stent. A cartilage graft was employed in the closure of the tracheostomy to produce fixation of the anterior wall.

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## ABSTRACTS

### AUTHORS' ABSTRACTS OF PAPERS PUBLISHED ELSEWHERE BY MEMBERS OF THE MOUNT SINAI HOSPITAL STAFF

Members of the hospital staff and the out patient department of the Mount Sinai Hospital are invited to submit for publication in this column brief abstracts of their articles appearing in other journals.

*Effect of Insulin Hypoglycemia on Gastric Secretion in Duodenal Ulcer and Controls.* A. WINKELSTEIN AND M. HESS. *Gastroenterology*, 11: 326, September, 1948.

Insulin hypoglycemia stimulates the dorsal vagus nucleus. This results in increased secretion of hydrochloride acid in the stomach. Since theoretic considerations suggest that the vagus nucleus may play an important role in the genesis of peptic ulcer, studies were directed to determine the role played by the dorsal vagus nucleus in the gastric secretory disturbance of duodenal ulcer. These studies demonstrated that 15 units of insulin given intravenously evokes a markedly higher, almost double, acidity response in duodenal ulcer patients than in normals. The results of these studies favor the addition of vagotomy to the surgical therapy of duodenal ulcer. These studies also suggest that it may be of fundamental importance in the problem of peptic ulcer therapy to find means of controlling the hyperirritability of the dorsal vagus nucleus. The possible relation of the blood sugar metabolism to the pathologic physiology of gastric secretion in peptic ulcer is also discussed.

*The Prevention and Interception of Malocclusion.* J. A. SALZMANN. *Am. J. Orthodontics*, 34: 9: 732, September, 1948.

Appliances inserted into the mouth at certain periods can be extremely harmful to the spontaneous tooth adjustments necessary for the establishment of normal occlusion. An example can be found when the maxillary permanent anterior teeth are completing their eruption and the maxillary central incisors are moving together while the maxillary lateral incisors are undergoing their final stages of eruption. Orthodontic therapy, whether or not it involves the use of mechanical appliances, should be undertaken as soon as it is recognized that a condition exists which interferes with normal growth, development, function, or relationship of the teeth and dental arches and there is little possibility of correction by further growth or developmental processes alone. As far as the use of appliances in orthodontics is concerned, it should be remembered that there is generally greater danger in "too much, too soon" rather than in "too little, too late."

*Gynecologic Surgery in the Elderly with Special Reference to Risks and Results.* F. D. ZEMAN, AND A. M. DAVIDS. *Am. J. Obst. & Gynec.*, 56: 456, September, 1948.

The increasing numbers of elderly women presenting a variety of gynecologic disorders bring new responsibilities to the gynecologist and to the internist. This study of 202 cases of women over 60 years of age who were subjected to 217 surgical procedures, with only 2 deaths, indicates that the range of surgery may be safely extended for this age group. Careful preoperative studies of these patients by the team of gynecologist and internist sharply limited the operative risk. These elderly women presented a variety of systemic conditions, associated with the local lesions. The implications of hypertension, arteriosclerotic heart disease, anemia, diabetes, and malnutrition have been discussed in relation to the determination of surgical risk. Modern methods of anesthesia, liberal use of whole blood transfusions, early rising, the use of chemotherapy and antibiotics prevented or modified complications of the postoperative period. In general, the authors believe that the careful evaluation of the functional capacity of older individuals will eliminate false emphasis on chronological age, and thus point the way to successful therapy.



*Gangliosympathectomy and Bilateral Hemiadrenalectomy for Severest Grade of Hypertension*  
H. NEUHOF. *Ann. Surg.* 128: 787, October, 1948.

Even the most radical forms of thoracolumbar sympathectomy do not often lead to satisfactory reduction of blood pressure. In these cases the author has added to the customary operation bilateral subtotal removal of the semilunar ganglia and bilateral removal of the upper halves (approximately) of the adrenal gland. The evolution of the operation is described. The results in the reported series of cases have been satisfactory. There has been no mortality and the operation appears to be as well tolerated as the less formidable one confined to the sympathetic nerves. The question is raised therefore as to whether the described operation should not be applied to less severe forms of hypertension in which, too, uniformity of results has not been obtained.

*The Incidence of Periodontal Disease in Children.* S. ZAPPLER AND P. PERSON. *New York J. Dent.*, 18: 300, October, 1948.

It is pointed out that periodontal disease (affecting alveolar bone, gingivae, periodontal membrane and other supporting elements of teeth) is more frequent in children and adolescents than is commonly believed. A statistical summary and wide geographical survey of the incidence of periodontal disease in children is presented in support of this concept. The importance of these observations to an understanding of periodontal physiology and pathology is discussed.

*Clinical Problems in Penicillin Sensitivity.* S. M. PECK, S. SIEGAL AND A. W. GLICK, AND A. KURTIN. *J.A.M.A.*, 138: 631, October, 1948.

Four hundred and six adults and 93 children were tested with penicillin and trichophytin. The reaction to the forty-eight-hour cutaneous test with penicillin was observed to possess clinical significance and practical diagnostic value. The technic of performing and reading this test is described. Other tests are presented and discussed, but their reactions were not found significant. Of 276 adults who had never had penicillin, 15, or 5.4 per cent, reacted "spontaneously" to the penicillin cutaneous test. Of 168 men, 11, or 6.5 per cent, reacted positively; of 108 women, 4, or 3.7 per cent, showed a positive reaction. Of 65 children, none reacted positively. The "spontaneous" reaction caused by penicillin sensitivity was three times as frequent among those patients who had a positive trichophytin reaction. Of 130 patients who received penicillin, 32 had cutaneous eruptions. Of these eruptions, 25 were of the urticarial serum-sickness-like type; 7 were of the erythematovesicular, trichophytid type. In 34.2 per cent of all men eruptions developed, whereas they occurred in only 8.3 per cent of women. In this group, all 17 positive reactions to penicillin cutaneous tests occurred in men, or 13.4 per cent of all patients. Of the 25 patients in the group with urticaria 21 were men and 4, women. Of these patients, 10 had a positive reaction to the cutaneous penicillin test, and 4 had a positive trichophytin reaction; all were men. A previous instance of fungous disease is not considered to play a role in this form of induced sensitivity. The 7 patients with the erythematovesicular type were men, each of whom had positive reactions to both the penicillin and the trichophytin test. The previous occurrence of fungous disease, which gave rise to penicillin sensitivity resulting in a "spontaneous" positive reaction to penicillin, is considered the basic mechanism of this type of sensitivity. The delayed reaction to the penicillin cutaneous test is of practical value in the diagnosis of "spontaneous" sensitivity; it serves as an aid in preventing generalized eruptions prior to penicillin therapy and as a guide to dosage for desensitization. Parenteral and oral methods of desensitization are described, and the results in 8 cases are presented.

*The Demonstration of  $P^{32}$  in Bone by Radioautography.* R. S. SIFFERT. *Science*, 108: 445, October, 1948.

In view of the facts that phosphorus is removed from bone on routine decalcification, and that detailed sections of undecalcified bone are not feasible, a method was sought to prepare bones of rabbits containing radioactive phosphorus for histological and radio-

autographic study. Following injections of  $P^{32}$  intravenously, bones of young rabbits were fixed in formalin and lead acetate, and decalcified in formic acid. Excellent radioautographs and histological sections were obtained. It was assumed that the phosphates liberated during decalcification were bound as lead salts that were insoluble in the decalcifying reagent, formic acid. Thereby, the  $P^{32}$  that had been metabolically deposited in the bone, remained bound at its site of liberation. Since thin sections could be cut, detailed autographs were obtained.

*Laboratory Procedures in the Study of Vagotomy—with Particular Reference to the Insulin Test.* F. HOLLANDER. *Gastroenterology*, 11: 419, October, 1948.

This paper is an attempt to answer some of the questions which have arisen concerning the insulin test used in the current study of vagotomy for peptic ulcer. The test shows the presence of functionally effective gastric secretory nerves. Regular insulin (20 units) is administered intravenously after collection of several control gastric specimens. One fasting and three post-insulin blood sugar determinations must be made; physical signs of hypoglycemia must not be used as criteria of an adequate hypoglycemia. Tests are invalid if blood sugars are above 50 mg/100 ml, or other test conditions have not been observed. A positive response to a valid insulin test is indicated if 2 or more free acid values are at least 20 mN above control values—unless controls are anacid by the histamine test, when a 10 mN rise is sufficient. A negative response is shown by the absence of such a rise, provided the patient is capable of secreting acid. Positive responses demonstrate persistence of some gastric secretory nerves; negative responses indicate complete parasympathetic gastric denervation. Total gastric acidity—as well as free acidity—may be of considerable importance in these tests, but further investigation is required to determine its significance.

*Emergency Psychotherapy in General Practice. The Doctor and the Patient; General Psychotherapeutic Considerations.* W. C. HULSE. *American Practitioner*, III: 2, October, 1948.

Some of the basic principles for psychotherapy with special emphasis on the interrelationship of physicians and patient are presented. The general practitioner has to accept the fact that a seemingly organic-syndrome may be psychogenic. Familiarity with the dynamisms underlying human behavior is essential for effective practice of psychotherapy. Complaints and symptoms produced by the emotional illness are rooted in the unconscious and the patient is unaware of his conflicts and of the mental origin of his symptoms. He is not a malingerer nor is his disorder "imaginary". Rapport, identification, transference, counter-transference and other concepts of dynamic psychiatry are discussed for the psychotherapeutically interested general practitioner. The importance of the doctor's own attitude and approach during physical examination and treatment, the use of supportive therapy and of reassurance and the limitations of these methods in patients with serious mental disturbances are stressed.

*DDT 2, Bis (p-chlorophenyl) 1, 1, 1-trichlorethane Poisoning.* J. H. GLOBUS. *J. Neuropath. & Exper. Neurol.*, 7: 418, October, 1948.

A number of monkeys, dogs, cats, and rats were subjected to DDT poisoning. The positive histopathological findings yielded by the study of all the material under investigation were meager and even these were of a highly doubtful significance. They consisted only of some reduction of the staining qualities of the tigroid substance in an isolated case, deformation of cell outline in the cerebral cortex of another case. This cannot be regarded as a reaction to the noxious agent, as similar changes were noted with equal frequency in the control animals. Much more significant were the observations that in no case was there an increase in the accumulation of free fat, nor was there an increase in glial elements. Nowhere were there encountered pathological glial elements, such as compound granular cells or an increase in microglia. In the absence of such alterations it may be con-

cluded that no significant changes took place in the morphology of the cellular elements of structures investigated. Hence, it may be said that all of the brains and spinal cords of the several species of animals studied disclosed no pathological alterations which could be regarded as resulting from the effects of DDT on the central nervous system. A question may be raised as to the adequacy of the total dosage employed and its competency to induce decisive morphologic changes but this must be left open until further investigations will provide the answer. Similarly, the material studied at the present offers no explanation for the convulsive seizures and the related neurologic manifestations exhibited by some of the animals exposed to DDT poisoning unless the drug may selectively affect the neuronal elements of the central nervous system, without causing recognizable morphologic alterations. It is conceivable that this may be established or excluded by histochemical methods, not yet available but highly desirable.

*Gargoylism (Lipochondrodystrophy).* MARTIN A. GREEN. *J. Neuropath & Exp. Neurol.*, 7: 399, October, 1948.

Gargoylism an uncommon heredito-degenerative disease, is distinguished clinically by the appearance in infancy or in early childhood of characteristic skeletal deformities and facial features associated with bilateral corneal opacities, mental deficiency, and hepatosplenomegaly. It is a fatal disease, death as the result of cardiac failure occurring usually before the patient reaches the age of 10 years. The most striking neuropathological findings are illustrated by a case of a 3 year old girl displaying typical clinical features of the disease. They included the following: internal hydrocephalus, widespread neuronal changes, such as marked swelling of the cell body and occasionally of the cell processes, disappearance of the tigroid substance, displacement of the nucleus, lack of endocellular fibrillae with dislocation of the few present to the periphery of the cell, the presence of numerous small, colorless vacuoles which stain with the Herxheimer scarlet red and the Nile blue methods. These changes were most pronounced in the cerebral cortex, the substantia nigra, the nuclei of the third and twelfth cranial nerves, and the anterior horns of the spinal cord. There was a strong similarity between these alterations and those encountered in the central nervous system in amaurotic family idiocy.

*Guided Liver Biopsy through Laparotomy Incision.* E. E. JEMERIN. *New York State J. Med.*, 48: 2276, October, 1948.

The determination of the presence of distant spread to the liver is of obvious significance in deciding the operability of intra-abdominal neoplasms. When laparotomy has been performed through a lower abdominal incision for a lesion of the pelvic viscera, one has to depend upon palpation for the interpretation of the significance of a nodule or nodules felt in the liver. This may be deceptive. However, a selective liver biopsy may be obtained once the abdomen has been opened by guiding into a palpated liver lesion an aspirating needle introduced through the upper abdominal or lower chest wall, a hand inserted into the abdomen through the original incision serving as the guide. The true nature of pathology felt in the liver may be determined in this manner with relative assurance that the selected area is being sampled definitively.

*Gaffky's Tetrads.* M. J. ORINGER. *Oral Surgery, Oral Medicine, and Oral Pathology.*, 1: 936, October, 1948.

The value of specialized laboratory facilities as diagnostic aids is emphasized in cases involving fevers of unknown origin accompanied by multiple confusing clinical symptoms. The clinical picture in this case was malaise, intermittent fever, 100-103.4°F. and intra-oral lesions resembling mucous patches, accompanied by cervical, axillary and inguinal adenopathy. Multiple lesions of tick and chigger bites were present, and a life-long history of work on dairy farms. Provisional diagnosis could be: secondary stage syphilis, tick, tularemia or undulant fever, non-specific stomatitis (associated with diabetes), or Vincents Stomatitis, despite absence of fetid odor. Laboratory tests for these dis-

eases all proved negative. Cultures were prepared from smears of the oral lesions, and pure colonies of Gaffky's tetrads (*M. Tetragenus*) isolated. These tetrads have been considered non-pathogenic for man, despite a report of septicemia by Fornaca in 1905, and indications that this micrococcus may be responsible for development of abscesses in the investing tissues around teeth.

*Hemolytic Anemia with Hemoglobinuria.* D. STATS, L. R. WASSERMAN, & N. ROSENTHAL. *Am. J. Clin. Path.*, 18: 10, October, 1948.

Twenty-five personally observed cases of acute hemolytic anemia with hemoglobinuria are analyzed and the data presented. There were 4 categories represented, namely, the Marchiafava-Micheli syndrome, cases caused by cold hemagglutinins or by drugs, and an idiopathic variety. The clinical and hematological criteria by which these cases may be differentiated are tabulated. Special immunological and spectroscopic techniques used in the study of these cases are described. It is indicated that splenectomy is not to be used in the treatment of these cases and, except for the Marchiafava-Micheli syndrome, the great value of blood transfusions is pointed out.

*Phosphorus Metabolism in Disseminated Sclerosis.* A. WEIL AND G. B. BRADBURN. *J. Neuropath. & Exper. Neurol.*, 7: 447, October, 1948.

While healthy males can balance phosphorus intake and output with a daily amount of about 2 grams, disseminated sclerosis patients retain approximately from 20 to 30 per cent of such a phosphorus intake. On the other hand, daily amounts of about 0.9 grams phosphorus are insufficient for healthy males and lead to a negative balance of about 20 per cent. Multiple sclerosis patients, however, are able to balance their phosphorus diet with this amount. The reasons responsible for phosphorus retention in disseminated sclerosis patients may be: elimination of large amounts of phospholipids of the nervous system from active metabolism; retention of phosphorus in other tissues (glia?); disturbance of phospholipid metabolism at one or more intermediary stages; lack of demand due to reduced muscular activity.

*Carcinomas of the Tongue in Monkeys and Pathologic Changes in the Central Nervous System.* H. KLUVER AND A. WEIL. *J. Neuropath. & Exper. Neurol.*, 7: 144, April, 1948.

Two cases of a carcinoma of the tongue in rhesus monkeys, one spontaneous and one transmitted, showed severe histopathologic changes of the motor nuclei of the brain stem and the spinal cord. These changes consisted in intracytoplasmic vacuoles, frequently containing a small roundish body, and other severe cell disease. This selective distribution is explained by citing Glakin's experiments which demonstrated direct connections between the lymphatic system of the pharynx and the subarachnoid spaces. It is assumed that the etiological factor responsible for the cellular damage (carcinoma toxins?, virus?) invaded the central nervous system via such lymphatics.

*The Role of the Vagus Nerves in the Medical and Surgical Therapy of Peptic Ulcer.* A. WINKELSTEIN. *New York State J. Med.*, 48: 2153, October, 1948.

Peptic ulcer, while probably a psychosomatic disease, seems to be mediated through the vagus nucleus and nerves. As evidence of this, the author has found that the vagus phase of gastric secretion is increased; that the nocturnal gastric secretion (vagal in origin) is increased; that the dorsal vagus nucleus is hyperirritable (as demonstrated by the Insulin Test), and that the persistent post-operative free acidity in 45 per cent of duodenal ulcer patients who have had a partial gastrectomy is vagal since it is abolished by atropine. The author has found that the only form of medical therapy which controls the increased, harmful night secretion is the continuous intragastric drip therapy during the night. In view of the importance of the vagus nerves in the problem of peptic ulcer therapy, vagotomy is regarded favorably. However, the conclusions of the group who have studied this at The Mount Sinai Hospital are as follows: Neither the good nor the bad results of



vagotomy are related to the completeness of the vagotomy. Bilateral vagotomy alone is not regarded favorably because of recurrences and many other untoward symptoms. The procedure which has given no recurrences to date and the highest percentages of post-operative achlorhydrias is a combination of partial gastrectomy with vagotomy. Gastroenterostomy combined with vagotomy is also being studied. These studies, particularly those dealing with the hyperirritability of the central vagus nucleus, suggest that further therapeutic attacks should be directed toward the possibility of allaying this central vagal hyperirritability.

*Studies in Pancreatic Function. Preliminary Series of Clinical Studies with the Secretin Test.* D. A. DREILING AND F. HOLLANDER. *Gastroenterology*, 11: 714, November, 1948.

The authors present a clinical study of pancreatic function in 145 patients. The method of performing the secretin test is discussed. Data from 93 "normals" are analyzed statistically and the findings compared with previously published series. The abnormal material is presented in four groups: 1. pancreatic carcinoma, 2. acute and chronic pancreatitis, 3. postcholecystectomy syndrome, 4. jaundice. The abnormalities of the secretin test observed in these groups are presented and evaluated. In addition, the use of secretin for secondary study of biliary tract function, especially in jaundice and post-cholecystectomy cases, is presented. A means of diagnosing partial obstruction of the common duct is introduced. The results of this study of pancreatic function with secretin confirm the impression of previous investigators that the test has great diagnostic potentialities.

*Pilonidal Disease, Management of Cysts, Sinuses and Abscesses in Naval Personnel.* E. GRANET AND L. K. FERGUSON. *Am. J. Surg.*, 70: 139, November, 1948.

Pilonidal inflammatory disease occurs commonly in the Navy. At the St. Alban's Naval Hospital 7.5 percent of all operations on the general surgical service during a recent 18 month period were performed for the eradication of this condition. In this paper the definitive surgical treatment of a continuous series of 319 cases was reviewed. Pilonidal cysts and sinuses originate in embryo from the neurogenic medullary canal, from infolding of the dorsal epidermis or from both. Three clinical types result: subcutaneous cyst alone, (neurogenic); sinuses or dimple alone, (epidermal); subcutaneous cyst communicating with sinuses, (neurogenic and epidermal). We find no convincing evidence to prove that hair grows from the epithelium of pilonidal cysts. We believe that external hair grows into the sinus, extends into the cyst, breaks off from the external root and in time is molded into "nests". Pilonidal inflammatory disease in our clinical cases occurred in four main types: (1) sinuses, (2) acute abscesses, (3) infected subcutaneous cyst and sinuses, and (4) infected subcutaneous cyst alone. Patients amenable to primary closure were operated upon under procaine-epinephrine local anesthesia. The infected cyst and sinus was carefully excised and the wound was closed with fine alloy steel approximating sutures reinforced by through-and-through tension sutures of heavier wire tied over gauze rolls. Only 5 of 50 patients so treated required more than three weeks for complete epithelization. The average healing time for all 50 patients was two and one half weeks. Cases necessitating wide excisions were partially closed by undermining the skin at the wound margins and suturing these to the post-sacral fascia, thereby minimizing the wound which is then allowed to heal by granulation. Acute abscesses were drained on admission. Revision operation 3 days later consisted of marsupialization of the wound saucerizing the margins thereof. Granulations in the base of the wound were curetted and healing allowed to proceed by granulation. In postoperative wounds following excision of pilonidal disease, daily meticulous wound toilet is necessary to attain healthy granulations and early epithelization.

## INDEX OF NUMBER 6, VOLUME SEVENTEEN

*In view of its special character, this number is indexed separately. The index of the remaining issues of this volume follows.*

The (\*) preceding the page number indicates an original article; the letters "ab" similarly placed indicate an abstract. Author entries are made only for original articles.

- ABDUCENS** nerve palsy following spinal anesthesia, \*1055
- Abscess, retro-cecal, a late sequela to acute gangrenous appendicitis, subphrenic, notes on, \*526
- Acids, fatty, x-ray diffraction analysis of mixtures containing sodium salts of, \*1048
- Aerographic studies, mucosal, of the stomach and small bowel, \*917
- Adelman, Milton H., and Lyons, Sidney S., Abducens nerve palsy following spinal anesthesia, \*1055
- Adlersberg, David, Bader, Leon D., and Trachtenberg, Harold, Observations on the use of the rice diet in the treatment of the ambulatory hypertensive patient, \*990
- Aged, the clinical picture of cerebral arteriosclerosis with particular reference to the, \*1075
- Anal canal, epidermoid carcinoma of the, \*478
- Anastomosis, method for the termino-venous and veno-arterious, \*506
- Anemia, hemolytic, with hemoglobinuria, (D. Stats, et al.), <sup>ab</sup>1131
- Anesthesia, spinal, abducens nerve palsy following, \*1055
- Appendicitis, acute gangrenous, retro-cecal abscess, a late sequela of, \*526
- acute, with malrotation of the caecum. Case report, \*563
- Arnheim, Ernest E., Dr. A. A. Berg. A memoir, \*351
- Surgery of the newborn, \*528
- Arterial embolism, peripheral, \*517
- Arteriosclerosis, cerebral, the clinical picture of, with particular reference to the aged, \*1075
- Arteriovenous anastomosis, direct, \*506
- Ascites, fibro-adenoma of the ovary with, and hydrothorax (Meigs' syndrome), \*596
- Asthenia, neurocirculatory, the psychosomatic approach to. A supplement to "The relation of neurocirculatory asthenia to anxiety neurosis", \*930
- the relation of neurocirculatory, to anxiety neurosis, \*924
- Atresia, congenital, of the bile ducts, \*552
- congenital, surgerv for deafness in, of the external auditory canal (with a report of a case), \*1104
- Aufses, Arthur, Pneumonectomy for primary localized lymphoma, \*693
- Avulsion of the diaphragm, \*463
- BABCOCK**, W. WAYNE, Direct arterio-venous anastomosis, \*499
- Bacon, Harry E., Venturo, R., and Sauer, I., Epidermoid carcinoma of the anal canal, \*478
- Bader, Leon, see Adlersberg, David, \*990
- Baehr, George, Scientific research in modern hospital practice, \*353
- Bakst, Alvin A., see Garlock, John H., \*450
- Ballistocardiography—a review, \*1060
- Bass, Murray H., Fetal defects resulting from viral disease of the pregnant mother, \*959
- Behrend, Albert, see Behrend, Moses, \*463
- Behrend, Moses, Behrend, Albert, and Rosenstein, Gladys, Avulsion of the diaphragm, \*463
- Bendick, Arthur J., Mucosal aerographic studies of the stomach and small bowel, \*917
- Berg, Dr. A. A., A memoir, an appreciation, \*351
- some of the principles and methods contributed by the service of, \*356
- Bernheim, Bertram, Towering men of medicine, \*369
- Bernstein, Solon S., and S. Mouchly Small, Psychodynamic factors in surgery, \*938
- Bile ducts, congenital atresia of the, \*552
- Bitschai, J., Calculosis of the urinary tract in Egypt, \*630
- Bladder, papillary carcinoma of the ureter and, thirteen years postnephrectomy for papillary carcinoma of the kidney, \*671
- primary closure of the, suprapubic prostatectomy with hemostasis by transurethral fulguration and, \*652
- Blood iodine and I-131 excretion in diagnostic problems of hyperthyroidism, \*781
- pressure, observations on, in children, following acute glomerulonephritis \*971
- transfusion, the romance of the modern era of, \*393
- Bloom, Samuel, see Goldman, Joseph L., \*1096
- Bowel, small, mucosal aerographic studies of the stomach and, \*917
- Burke, Louis, Davids, Arthur, and Seley, Gabriel, Torsion of the fallopian tube producing gangrene of the small intestine, \*605
- CAECUM**, malrotation of the, acute appendicitis with. Case report, \*563
- Calculosis of the urinary tract in Egypt, \*630

- Cancer, recurrent cervical metastatic, \*618  
the present status of the surgical treatment of, of the colon and rectum, \*486
- Carcinoma, epidermoid, of the anal canal, \*478  
gall bladder, of the, \*467  
papillary, of the kidney, papillary carcinoma of the ureter and bladder, thirteen years postnephrectomy for, \*671  
tongue, of the, in monkeys and pathologic changes in the central nervous system, (H. Klüver and A. Weil), <sup>ab</sup>1131
- Clinical problems in penicillin sensitivity, (S. Peck, et al.), <sup>ab</sup>1128
- Closure, of pharyngostome by distant open lined flap, \*1096  
primary, suprapubic prostatectomy with hemostasis by transurethral fulguration and, of the bladder, \*652
- Cohen, Ira, Tumors of the intracranial portion of the optic nerve, \*738
- Colectomy, cesarian section after, for ulcerative colitis, \*610
- Colitis, ulcerative, cesarian section after colectomy for, \*610
- Colon, the present status of the surgical treatment of cancer of the, and rectum, \*486
- Colp, Ralph, see Klingenstein, Percy, \*429
- Constipation, chronic, observations on the use of digitalis in the treatment of, and allied conditions, \*980
- Cornell, Albert, Changes in gastric acidity and motility in a case of bilateral subphrenic vagotomy alone for duodenal ulcer (11 year follow-up of immediate and late results), \*855
- Crohn, Burrill, Gastroenterology as a surgical specialty at The Mount Sinai Hospital, \*843
- D**ANZIS, Max, Carcinoma of the gall bladder, \*467
- Dauids, Arthur, see Burke, Louis, \*605
- DDT 2, Bis (p-chlorophenyl) 1,1,1-trichloroethane poisoning, (J. H. Globus), <sup>ab</sup>1129
- Deafness, surgery for, in congenital atresia of the external auditory canal (with a report of a case), \*1104
- Decortication, pulmonary, in civilian practice, \*680
- De Lange, Sam, and Kohn, Jerome L., Observations on blood pressure in children following an acute glomerulo-nephritis, \*971
- Demonstration of P<sup>32</sup> in bone by radioautography, (R. Siffert), <sup>ab</sup>1128
- Diaphragm, avulsion of the, \*463
- Digitalis, observations on the use of, in the treatment of chronic constipation and allied conditions, \*980
- Doubilet, Henry, and Mulholland, John H., The results of sphincterotomy in pancreatitis, \*458
- Druckerman, Leonard J., see Klingenstein, Percy, \*429
- Duodenal ulcer, effect of insulin hypoglycemia on gastric secretion in, and controls, (A. Winkelstein and M. Hess), <sup>ab</sup>1127
- Duodenum, multiple erosions and acute perforations of the esophagus, stomach, and, in relation to disorders of the nervous system, \*817
- E**DELMAN, LEO, Lipomyosarcoma of the kidney: A report of two cases, \*659
- Effect of insulin hypoglycemia on gastric secretion in duodenal ulcer and controls, (A. Winkelstein and M. Hess), <sup>ab</sup>1127
- Egypt, Calculosis of the urinary tract in, \*630
- Elderly, gynecological surgery in the, with special reference to risks and benefits, (F. Zeman and A. Davids), <sup>ab</sup>1127
- Embolism, peripheral arterial, \*517
- Endometriosis in a laparotomy scar. Report of a case with utero-abdominal fistula, \*613
- Epstein, Albert A., Observations on the use of digitalis in the treatment of chronic constipation and allied conditions, \*980
- Erosions, multiple, and acute perforations of the esophagus, stomach, and duodenum in relation to disorders of the nervous system, \*817
- Esophagus, multiple erosions and acute perforations of the stomach, and duodenum in relation to disorders of the nervous system, \*817
- Excision, simple, the treatment of pterygium by, \*1092
- Excretion, blood iodine and I-131, in diagnostic problems of hyperthyroidism, \*781
- External auditory canal, surgery for deafness in congenital atresia of the, (with a report of a case), \*1104
- F**ALLOPIAN tube, torsion of the, producing gangrene of the small intestine, \*605
- Felshin, Gertrude, Acute appendicitis with malrotation of the caecum. Case report, \*563
- Fetal defects resulting from viral disease of the pregnant mother, \*959
- Fibro-adenoma of the ovary with ascites and hydrothorax (Meigs' syndrome), \*596
- Fieber, Mack H., see Silver, Solomon, \*781
- Finsterer, Hans, Surgical treatment in acute hemorrhage of peptic ulcers, \*377
- Fistulas, vagotomy and subtotal gastric resection with vagotomy in cases of gastrojejunal and gastrojejuno-colic ulcers and, after multiple previous surgical procedures, \*423
- Fracture, depressed, of the tibial plateau, \*761
- G**AFFKY'S tetrads, (M. Oringer), <sup>ab</sup>1130
- Gaines, Joseph A., see Mintz, Nathan, \*613
- Gall bladder, carcinoma of the, \*467

- Gangliosympathectomy and bilateral hemi-adrenalectomy for severest grade of hypertension, (H. Neuhoof), <sup>ab</sup>1128
- Gangrene of the small intestine, torsion of the fallopian tube producing, \*605
- Garbat, A. L., The simultaneous occurrence of active peptic ulcer and active hyperthyroidism, \*787
- Gargoylism (Lipochondrodystrophy), (M. Green), <sup>ab</sup>1130
- Garlock, John H., and Bakst, Alvin A., Pudendal hernia. Report of a case operated upon by the abdominal route, \*450
- Gastrectomy, observations on, for chronic duodenal ulcer with particular reference to gastrectomy with and without infradiaphragmatic vagotomy, \*429
- Gastric acidity, changes in, and motility in a case of bilateral subphrenic vagotomy alone for duodenal ulcer (11 year follow-up of immediate and late results), \*855
- lesions, high, preservation of the pyloric antrum in resection of, \*442
- pouch, the, from its origin to the present. (An historical study in the methodology of gastric physiological research, with particular reference to the contributions of Pavlov), \*872
- secretion in duodenal ulcer and controls, effect of insulin hypoglycemia on, (A. Winkelstein and M. Hess), <sup>ab</sup>1127
- Gastroenterology as a surgical specialty in The Mount Sinai Hospital, \*843
- Gertler, Menard M., see Oppenheimer, B.S., \*924
- Ginzburg, Leon, Some of the principles and methods contributed by the service of Dr. A. A. Berg, \*356
- Glickman, Stanley I., see Hyman, Abraham, \*652
- Globus, Joseph H., and Ralston, Bruce, Multiple erosions and acute perforations of the esophagus, stomach, and duodenum in relation to disorders of the nervous system, \*817
- Glomerulo-nephritis, acute, observations on blood pressure in children, following, \*971
- Goldberger, Morris A., and Zakin, David, Prolapse of the uterus. A review of 722 cases treated by the parametrial fixation operation, \*571
- Goldman, Joseph L., and Bloom, Samuel, Closure of pharyngostome by distant open lined flap, \*1096
- Gross, Sidney W., Spontaneous occlusion of the internal carotid artery in the neck, \*746
- Grossman, M. I., see Janowitz, Henry D., \*1004
- Grossman, Sidney, Surgical aspects of peptic ulcer, \*848
- Gynecologic surgery in the elderly with special reference to risks and results, (F. Zeman and A. Davids), <sup>ab</sup>1127
- HARRIS, WILLIAM, see Silverstone, Sidney, \*1083
- Hematology, the use of radioactive and stable isotopes in, \*1037
- Hemiadrenalectomy, bilateral, and gangliosympathectomy, for severest grades of hypertension, (H. Neuhoof), <sup>ab</sup>1128
- Hemoglobinuria, hemolytic anemia with, (D. Stats et al.), <sup>ab</sup>1131
- Hemolytic anemia with hemoglobinuria, (D. Stats et al.), <sup>ab</sup>1131
- Hemorrhage, active, retroperitoneal sarcoma (adrenal tumor?) with. A surgical emergency resection. Twenty-seven year follow-up, \*520
- Hemorrhages, acute, surgical treatment in, of peptic ulcers, \*377
- Hemorrhagic, primary, segmental, idiopathic infarction of the greater omentum, \* 523
- Hemostasis, suprapubic prostatectomy with, by transurethral fulguration and primary closure of the bladder, \*652
- technical principles in myomectomy with special reference to, \*565
- Hernia, pudendal. Report of a case operated upon by the abdominal route, \*450
- Hess, Elmer, Roth, Russell B., and Kaminisky, Anthony F., Renal ptosis, \*644
- Historical study, an, in the methodology of gastric physiological research, with particular reference to the contributions of Pavlov. The gastric pouch from its origin to the present, \*872
- Hollander, Franklin, The gastric pouch from its origin to the present (An historical study in the methodology of gastric physiological research, with particular reference to the contributions of Pavlov), \*872
- Hoon, James R., see Walters, Waltman, \*423
- Hospital practice, modern, scientific research in, \*353
- Hydrothorax, fibro-adenoma of the ovary with ascites and, (Meigs' syndrome), \*596
- Hyman, Abraham, Leiter, H. Evan, and Glickman, Stanley I., Suprapubic prostatectomy with hemostasis by transurethral fulguration and primary closure of the bladder, \*652
- Hyperparathyroidism, \*774
- Hypertension, gangliosympathectomy and bilateral hemi-adrenalectomy for severest grade of, (H. Neuhoof), <sup>ab</sup>1128
- Hypertensive patient, observations on the use of the rice diet in the treatment of the ambulatory, \*990
- Hyperthyroidism, active, the simultaneous occurrence of active peptic ulcer and, \*787
- blood iodine and I-131 excretion in diagnostic problems of, \*781
- INCIDENCE of periodontal disease in children, (S. Zappler and P. Person), <sup>ab</sup>1128



- Infarction, primary segmental, idiopathic, hemorrhagic, of the greater omentum, \*523
- Insulin, hypoglycemia, effect of, on gastric secretion in duodenal ulcer and controls, (A. Winkelstein and M. Hess), <sup>ab</sup>1127
- test, laboratory procedures in the study of vagotomy—with particular reference to, (F. Hollander), <sup>ab</sup>1129
- Intestine, malrotation of the, \*886
- small, melanoma of the, and stomach, \*907
- small, torsion of the fallopian tube producing gangrene of the, \*605
- Iodine, blood, and I-131 excretion in diagnostic problems of hyperthyroidism, \*781
- Isotopes, the use of radioactive and stable, in hematology, \*1037
- JAFFE, HARRY L.**, see Master, Arthur M., \*934
- Jaffin, Abraham E., Fibro-adenoma of the ovary with ascites and hydrothorax (Meigs' syndrome), \*596
- Janowitz, Henry D., and Grossman, M. L., A simple test for extent of sympathectomy, \*1004
- Jejunum, preliminary results of vagotomy in the treatment of peptic ulcer near the cardia and of peptic ulcer of the, (marginal ulcer, stomal ulcer), \*409
- KAMINSKY, ANTHONY F.**, see Hess, Elmer, \*644
- Kaufman, Herman S., see Mayer, Gerda Gersheim, \*1048
- Kidney, congenital ectopic hydronephrotic, simulating an intraperitoneal lesion, \*675
- lipomyosarcoma of the: Report of two cases, \*659
- papillary carcinoma of the ureter and bladder thirteen years post-nephrectomy for papillary carcinoma of the, \*671
- Klein, Samuel H., The present status of the surgical treatment of cancer of the colon and rectum, \*486
- Klemme, Roland M., Bilateral trigeminal neuralgia, \*729
- Klemperer, Paul, Changing patterns in the definition of acute lupus erythematosus, \*793
- Klempner, Emanuel, Cesarean section after colectomy for ulcerative colitis, \*610
- Klingenstein, Percy, Colp, Ralph, Druckerman, L., and Weinstein, Vernon, Observations on gastrectomy for chronic duodenal ulcer with particular reference to gastrectomy with and without infradiaphragmatic vagotomy, \*429
- Kohn, Jerome L., see de Lange, Sam, \*971
- Kross, Isidor, and Rosenblatt, Milton B., The middle lobe syndrome, \*711
- LABORATORY** procedures in the study of vagotomy—with particular reference to the insulin test, (F. Hollander), <sup>ab</sup>1129
- de Lange, Sam, and Kohn, Jerome L., Observations on blood pressure in children following an acute glomerulo-nephritis, \*971
- Laparotomy incision, guided liver biopsy through, (E. Jemerin), <sup>ab</sup>1130
- scar, endometriosis in a. Report of a case with utero-abdominal fistula, \*613
- Larynx, reconstruction of the, and the trachea. Report of a case of extensive cicatricial stenosis, \*1117
- Lear, Harold, see Oppenheimer, Gordon, \*671
- Lee, S., see Rosenthal, Nathan, \*1008
- Leiter, H. Evan, see Hyman, Abraham, \*652
- Lewisohn, Richard, The romance of the modern era of blood transfusion, \*393
- Lipochoondrodystrophy, gargoylism, (M. Green), <sup>ab</sup>1130
- Lipoma petrificum ossificans or lipoma with heterotopia ossification, \*769
- Lipomyosarcoma of the kidney. Report of two cases, \*659
- Lippmann, Robert, Depressed fracture of the tibial plateau. A simple surgical method for elevation and fixation of the depressed fragment, \*761
- Lipsay, Joan, see Richman, Alexander, \*907
- see Rosenthal, Nathan, \*1008
- Liver biopsy guided through, laparotomy incision, (E. Jemerin), <sup>ab</sup>1130
- Lupus erythematosus, acute, changing patterns in the definition of, \*793
- Lymphoma, pneumonectomy for primary localized, \*693
- Lyons, Sidney S., see Adelman, Milton H., \*1055
- MALIGNANCY**, a survey of some recently proposed chemical tests for, \*1021
- Malocclusion, prevention and interreception of, (J. Salzman), <sup>ab</sup>1127
- Malrotation of the intestine, \*886
- Mandl, Felix, Vagotomy in the treatment of peptic ulcer near the cardia and the peptic ulcer of the jejunum, (Marginal ulcer, stomal ulcer), \*409
- Margolin, Sidney G., The psychosomatic approach to neurocirculatory asthenia—a supplement to "The relation of neurocirculatory asthenia to anxiety neurosis", \*936
- Master, Arthur M., and Jaffe, Harry L., The cardiac patient and operation, \*934
- Mayer, Gerda Gersheim, Kaufman, Herman S., and Peck, Samuel M., X-ray diffraction analysis of mixtures containing sodium salts of fatty acids, \*1048
- Medicine, towering men of, \*369

Meigs' syndrome, fibro-adenoma of the ovary with ascites and hydrothorax, \*596

Melanoma of the small intestine and stomach, \*907

Ménière's disease, what is justifiable surgically in?, \*1109

Metabolism, phosphorus, in disseminated sclerosis, (A. Weil and G. Bradburne), <sup>ab</sup>1131

Middle lobe syndrome, the, \*711

Mintz, Nathan, and Gaines, Joseph A., Endometriosis in a laparotomy scar. Report of a case with utero-abdominal fistula, \*613

Moschcowitz, Eli, Sarcoidosis in relation to tuberculosis, \*799

Motility, changes in gastric acidity and, in a case of bilateral subphrenic vagotomy alone for duodenal ulcer (11 year follow-up of immediate and late results), \*855

Muholland, John H., see Doubilet, Henry, \*458

Myomectomy, technical principles in, with special reference to hemostasis, \*565

**N**ERVOUS system, multiple erosions and acute perforations of the esophagus, stomach, and duodenum in disorders of the, \*817

Neuhof, Harold, Retroperitoneal sarcoma (adrenal tumor?) with active hemorrhage. A surgical emergency resection. Twenty-seven year follow-up, \*520

Neuralgia, bilateral trigeminal, \*729

Neuroblastoma, the treatment of, \*1083

Neurocirculatory asthenia, the psychosomatic approach to—a supplement to "The relation of neurocirculatory asthenia to anxiety neurosis", \*930

the relation of, to anxiety neurosis, \*924

Neurosis, anxiety, the relation of neurocirculatory asthenia to, \*924

Newborn, surgery of the, \*528

Nissen, Rudolph, Preservation of the pyloric antrum in resection of high gastric lesions, \*442

**O**BSTRUCTION, intestinal, complicated by pregnancy, \*625

Occlusion, spontaneous, of the internal carotid artery in the neck, \*746

Omentum, greater, primary segmental idiopathic, hemorrhagic infarction of the, \*523

Operation, consent for, \*373

the cardiac patient and, \*934

Oppenheimer, B. S., and Gertler, Menard M., The relation of neurocirculatory asthenia to anxiety neurosis, \*924

Oppenheimer, Gordon, and Lear, Harold, Papillary carcinoma of the ureter and bladder thirteen years post-nephrectomy for papillary carcinoma of the kidney, \*671

Optic nerve, intracranial portion of the, tumors of the, \*738

Ossification, lipoma petrificum ossificans or lipoma with heterotopia, \*769

Osteoplastic exposure, an improved, of the temporo-occipital region, \*750

Ovary, fibro-adenoma of the, with ascites and hydrothorax, (Meigs' syndrome), \*596

**P**-32 demonstration of, in bone, by radioautography, (R. Siffert), <sup>ab</sup>1128

Palsy, abducens nerve, following spinal anesthesia, \*1055

Pancreatic function, studies in. Preliminary series of clinical studies with the secretin test, (D. Dreiling and F. Hollander), <sup>ab</sup>1132

Pancreatitis, the results of sphincterotomy in, \*458

Paolucci, R., and Tosatti, E., Method for the termino-venous and veno-arterious anastomosis, \*506

Parametrial fixation operation, a review of 722 cases treated by the. Prolapse of the uterus, \*571

Pavlov, an historical study in the methodology of gastric physiological research, with particular reference to the contributions of. The gastric pouch from its origin to the present, \*872

Peck, Samuel M., see Mayer, Gerda Gershein, \*1048

Penicillin sensitivity, clinical problems in, (S. Peck et al.), <sup>ab</sup>1128

Peptic ulcer, role of the vagus nerve in the medical and surgical therapy of, (A. Winkelstein), <sup>ab</sup>1131

Perforations, acute, multiple erosions and, of the esophagus, stomach, and duodenum in relation to disorders of the nervous system, \*817

Periodontal disease in children, incidence of, (S. Zappier and P. Person), <sup>ab</sup>1128

Pharyngostome, closure of, by distant open lined flap, \*1096

Phosphorus metabolism in disseminated sclerosis, (A. Weil and G. Bradburne), <sup>ab</sup>1131

Pilonidal disease, management of cysts, sinuses and abscesses in naval personnel, (E. Granet and L. Ferguson), <sup>ab</sup>1132

Pleuropneumectomy, extrapleural pulmonary resection, \*700

Pneumectomy for primary localized lymphoma, \*693

Poisoning, DDT 2, Bis (p-chlorophenyl) 1,1,1-trichloroethane, (J. H. Globus), <sup>ab</sup>1129

Pollock, Leo H., Malrotation of the intestine, \*886

Pregnancy, intestinal obstruction complicated by, \*625

Pregnant mother, fetal defects resulting from viral disease of the, \*959

Prevention and interception of malocclusion, (J. Salzman), <sup>ab</sup>1127

Prolapse of the uterus. A review of 722 cases treated by parametrial fixation operation, \*571

- Prostatectomy, suprapubic, with hemostasis by transurethral fulguration and primary closure of the bladder, \*652
- Psychodynamic factors in surgery, \*938
- Psychosomatic approach, the, to neurocirculatory asthenia—a supplement to "The relation of neurocirculatory asthenia to anxiety neurosis", \*930
- Psychotherapy emergency in general practice. The doctor and the patient; general psychotherapeutic considerations, (W. Hulse), <sup>ab</sup>112
- Pterygium, the treatment of, by simple excision, \*1092
- Ptosis, renal, \*644
- Pulmonary resection, extrapleural, (pleuropneumonectomy), \*700
- Purpura hemorrhagica, recurrent, the role of accessory spleens in post-splenectomy, \*1008
- Pyloric antrum, preservation of, in resection of high gastric lesion, \*442
- R**ABIN, COLEMAN B., Notes on subphrenic abscess, \*717
- Radioautography, demonstration of P<sup>32</sup> in bone by, (R. Siffert), <sup>ab</sup>1128
- Ralston, Bruce, see Globus, Joseph H., \*817
- Rashoff, Ira A., see Wasserman, Louis R., \*1037
- Rectum, the present status of the surgical treatment of cancer of the colon and, \*486
- Research, scientific, in modern hospital practice, \*353
- Resection, vagotomy and subtotal gastric, with vagotomy in cases of gastrojejunal and gastrojejunocolic ulcers and fistulas after multiple previous surgical procedures, \*423
- Rice diet, observations on the use of, in the treatment of the ambulatory hypertensive patient, \*990
- Richman, Alexander, and Lipsay, Joan, Melanoma of the small intestine and stomach, \*907
- Role of the vagus nerves in the medical and surgical therapy of peptic ulcer, (A. Winkelstein), <sup>ab</sup>1131
- Rosen, Samuel, Surgery for deafness in congenital atresia of the external auditory canal (with a report of a case), \*1104
- Rosenblatt, Milton N., see Kross, Isidor, \*711
- Rosenstein, Gladys, see Behrend, Moses, \*463
- Rosenthal, D., see Snapper, I., \*774
- Rosenthal, Nathan, Vogel, P., Lee, S., and Lipsay, Joan, The role of accessory spleens in post-splenectomy recurrent purpura hemorrhagica, \*1008
- Rosenwasser, Harry, What is justifiable surgically in Ménière's disease?, \*1109
- Roth, Russell B., see Hess, Elmer, \*644
- Rubin, I. C., Technical principles in myomectomy with special reference to hemostasis, \*565
- S**ALTS, sodium, x-ray diffraction analysis of mixtures containing, of fatty acids, \*1048
- Saltzstein, Harry C., Recurrent cervical metastatic cancer, \*618
- Sarcoidosis, in relation to tuberculosis, \*799
- Sarcoma, retroperitoneal, (adrenal tumor?) with active hemorrhage. A surgical emergency resection. Twenty-seven year follow-up, \*520
- Sarot, Irving A., Extrapleural pulmonary resection (pleuropneumonectomy), \*700
- Sauer, I., see Bacon, Harry E., \*478
- Schein, Albert J., Lipoma petrificum ossificans or lipoma with heterotopia ossification, \*769
- Schlesinger, Benno, An improved osteoplastic exposure of the temporo-occipital region, \*750
- Sclerosis, disseminated, phosphorus metabolism in, (A. Weil and G. Bradburne), <sup>ab</sup>1131
- Secretin test, preliminary series of clinical studies with. Studies in pancreatic function, (D. Dreiling and F. Hollander), <sup>ab</sup>1132
- Seley, Gabriel, Primary segmental idiopathic hemorrhagic infarction of the greater omentum, \*523
- see Burke, Louis, \*605
- see Touroff, Arthur S. W., \*680
- Silbert, Samuel, Peripheral arterial embolism, \*517
- Silver, Solomon, Yohalem, Stephen B., and Fieber, Mack H., Blood iodine and I-131 excretion in diagnostic problems of hyperthyroidism, \*781
- Silverstone, Sidney, and Harris, William, The treatment of neuroblastoma, \*1083
- Small, Mouchly S., see Bernstein, Solon, \*938
- Snapper, I., and Rosenthal, D., Hyperparathyroidism, \*774
- Sobotka, Harry, A survey of some recently proposed chemical tests for malignancy \*1021
- Som, Max L., Reconstruction of the larynx and the trachea. A report of a case of extensive cicatricial stenosis, \*1117
- Sphincterotomy, the results of, in pancreatitis, \*458
- Spleens, accessory, the role of, in post-splenectomy recurrent purpura hemorrhagica, \*1008
- Stenosis, cicatricial, report of a case of. Reconstruction of the larynx and the trachea, \*1117
- Stieglitz, Leopold, Dr. A. A. Berg: An appreciation, \*370
- Stomach, melanoma of the small intestine and, \*907
- mucosal aerographic studies of the, and small bowel, \*917



- multiple erosions and acute perforations of the esophagus, and duodenum in relation to disorders of the nervous system, \*817
- Strauss, Alfred A., Congenital atresia of the bile ducts, \*552
- Studies in pancreatic function, Preliminary series of clinical studies with the secretin test, (D. Dreiling and F. Hollander), <sup>ab</sup>1132
- Sullivan, Thomas J., Retro-cecal abscess, a late sequela of acute gangrenous appendicitis, \*526
- Surgery for deafness in congenital atresia of the external auditory canal (with report of a case), \*1104
- of the newborn, \*528
- psychodynamic factors in, \*938
- Swick, Moses, Congenital ectopic hydronephrotic kidney simulating an intraperitoneal lesion, \*675
- Sympathectomy, a simple test for the extent of, \*1004

**TEMPORO-OCCIPITAL** region, an improved osteoplastic exposure of the, \*750

- Tetrads, Gaffky's, (M. Oringer), <sup>ab</sup>1130
- Therapies, present day medical—peptic ulcer, \*808
- Tibial plateau, depressed fracture of the, \*761
- Tongue, carcinoma of, in monkeys and pathologic changes in the central nervous system, (H. Klüver and A. Weil), <sup>ab</sup>1131
- Torsion of the fallopian tube producing gangrene of the small intestine, \*605
- Tosatti, E., see Paolucci, R., \*506
- Touroff, Arthur S. W. and Seley, Gabriel, Pulmonary decortication in civilian practice, \*680
- Trachea, reconstruction of the larynx and the. Report of a case of extensive cicatricial stenosis, \*1117
- Trachtenberg, Harold, see Adlersberg, David, \*990
- Transfusion, blood, the romance of the modern era of, \*393
- Transurethral fulguration, suprapubic prostatectomy with hemostasis by, and primary closure of the bladder, \*652
- Treatment, surgical, the present status of the, of cancer of the colon and rectum, \*486
- Trigeminal neuralgia, bilateral, \*729
- Tuberculosis, the relation of sarcoidosis to, \*799
- Tumors of the intracranial portion of the optic nerve, \*738
- Turner, Joseph, Consent for operation, \*373
- Turner, Louis B., Ballistocardiography—A review, \*1060

**ULCER**, active peptic, the simultaneous occurrence of, and active hyperthyroidism, \*787

chronic, duodenal, observations on gas-

- trectomy for, with particular reference to gastrectomy with and without infradiaphragmatic vagotomy, \*429
- duodenal, changes in gastric acidity and motility in a case of bilateral subphrenic vagotomy alone for, (11 year follow-up of immediate and late results), \*855
- marginal, preliminary results of vagotomy in the treatment of peptic ulcer near the cardia and of peptic ulcer of the jejunum, \*409
- peptic, present day medical therapies, \*808
- peptic, surgical aspects of, \*848
- stomach, preliminary results of vagotomy in the treatment of peptic ulcer near the cardia and of peptic ulcer of the jejunum, \*409
- Ulcers, gastrojejunal and gastrojejunocolic, vagotomy and subtotal gastric resection with vagotomy in cases of, and fistulas after multiple previous surgical procedures, \*423
- peptic, surgical treatment in acute hemorrhages in, \*377
- Ureter, papillary carcinoma of the, and bladder thirteen years post-nephrectomy for papillary carcinoma of the kidney, \*671
- Urinary tract, calculus of the, in Egypt, \*630
- Utero-abdominal fistula, report of a case with. Endometriosis in a laparotomy scar, \*613
- Uterus, prolapse of the. Review of 722 cases treated by the parametrial fixation operation, \*571

- VAGOTOMY**, infradiaphragmatic, observations on gastrectomy for chronic duodenal ulcer with particular reference to gastrectomy with and without, \*429
- laboratory procedures in the study of—with particular reference to the insulin test, (F. Hollander), <sup>ab</sup>1129
- preliminary results of, in the treatment of peptic ulcer near the cardia and of peptic ulcer of the jejunum, \*409
- subphrenic, changes in gastric acidity and motility in a case of bilateral alone for duodenal ulcer (11 year follow-up of immediate and late results), \*855
- subtotal resection with vagotomy in cases of gastrojejunal and gastrojejunocolic ulcers and fistulas after multiple previous surgical procedures, \*423
- Vagus nerves, role of the, in the medical and surgical therapy of peptic ulcer, (A. Winkelstein), <sup>ab</sup>1131
- Venturo, R., see Bacon, Harry E., \*478
- Viral disease, fetal defects resulting from, in the pregnant mother, \*959
- Vogel, P., see Rosenthal, N., \*1008

**WALTER**, ROBERT I., Intestinal obstruction complicated by pregnancy, \*625



- Walters, Waltman, and Hoon, James R., Vagotomy and subtotal gastric resection with vagotomy in cases of gastrojejunal and gastrojejunocolic ulcers and fistulas after multiple previous surgical procedures, \*423
- Wasserman, Louis R., Rashoff, Ira A., and Yoh, T. F., The use of radioactive and stable isotopes in hematology, \*1037
- Weinstein, Vernon, See Klingenstein, Percy, \*429
- Wexler, David, The treatment of pterygium by simple excision, \*1092
- Winkelstein, Asher, Peptic ulcer—present day medical therapies, \*808
- X**-RAY diffraction analysis of mixtures containing sodium salts of fatty acids, \*1048
- Y**OH, T. F., see Wasserman, Louis, \*1037
- Yohalem, Stephen B., see Silver, Solomon, \*781
- Z**AKIN, DAVID, see Goldberger, Morris A., \*571
- Zeman, Frederick D., The clinical picture of cerebral arteriosclerosis with particular reference to the aged, \* 1075

# INDEX TO VOLUME SEVENTEEN

Numbers 1, 2, 3, 4, & 5

[In view of its special character, number 6 of this volume is indexed separately on pages immediately preceding this index.]

The (\*) preceding the page number indicates an original article; the letters "ab" similarly placed indicate an abstract, while "br" similarly placed indicates book review. Author entries are made only for original articles.

- A**BERRANT insertion of pulmonary veins, \*336
- Abscess, perianal, is anal fistula a necessary sequel to?, (E. Granet), <sup>ab</sup>69
- Acidity, gastric, effect of physically induced pyrexia on, (J. Bandes, et al.), <sup>ab</sup>75
- Aene vulgaris, photosensitization of, (A. Kurtin and R. Yontef), <sup>ab</sup>268
- Action of curare on erythrine alkaloids on morphinized mice, (E. P. Pick and G. V. Richards), <sup>ab</sup>76
- Adhesive tape, a new, remover of particular value in patch testing, (A. Glick, et al.), <sup>ab</sup>346
- Adrenergic component in the nervous mechanism of sweating in man, evidence for, (H. Haimovici), <sup>ab</sup>147
- Air, alveolar, PII of gastric mucous secretion with, (F. Hollander and F. U. Lauber), <sup>ab</sup>73
- Alcoholic service, medical aspects of, in a general hospital, (M. Texon), <sup>ab</sup>208
- Alexander, R. M., Gallstone obstruction of the duodenum: case report, \*183
- Allergies, physical, whealing response to light and cold with a note on the mechanisms and origin of, (H. A. Abramsen), <sup>ab</sup>72
- 4-amino-2-methyl-L-naphthol hydrochloride, properties of, (G. Schwartzman), <sup>ab</sup>74
- Amputations, mid-leg, for gangrene in the diabetic, (S. Silbert), <sup>ab</sup>75
- Amyloid disease of the urinary bladder, \*254
- Anal chronic fissure, surgical treatment of, (R. Turell), <sup>ab</sup>77
- plastic repair for postoperative incontinence, (R. Turell), <sup>ab</sup>345
- $\Delta$  3, 5 androstadienone-17 in the urine, ultra-violet spectrophotometric method for the determination of, \*98
- Anemia and polycythemia on digital intravascular blood viscosity, effect of, (M. Mendlowitz), <sup>ab</sup>349
- Anesthesia, intracranial novocain, in frogs, (B. Kisch), <sup>ab</sup>267
- thoracic surgery, in, with special reference to surgery of the esophagus, (S. Lyons), <sup>ab</sup>349
- Angina, grave de petto per nove anni, con minime alterazioni elettrocardiografiche. Esito dovuto a insufficienza coronarica senza infart (secondaria a pancreatite acuta emorragica), (M. Volterra), <sup>ab</sup>348
- Angiocardiography, and cardiac catheterization, technique of, as employed at The Mount Sinai Hospital, \*272
- Angiofibroma, juvenile nasopharyngeal, (H. E. Ehrlich, et al.), <sup>ab</sup>72
- Angiogenesis, with reference to Laennec cirrhosis, its histogenesis, (E. Moschcowitz), <sup>ab</sup>71
- Another occupational mark, \*44
- Antibacterial properties of 4-amino-2-methyl-L-naphthol hydrochloride, (G. Schwartzman), <sup>ab</sup>74
- Antibodies, role of, in insulin resistance, \*102
- Apical systolic murmur, (A. M. Master), <sup>ab</sup>76
- Arai, Harold S., see Leon J. Pordy, \*26
- Arches, basal, orthodontic therapy as limited by ontogenetic growth and the, (J. A. Salzmann), <sup>ab</sup>75
- Arteriography, cerebral, (S. N. Gross), <sup>ab</sup>75
- cerebral, in subarachnoid hemorrhage, (I. S. Wechsler and S. W. Gross), <sup>ab</sup>72
- Artery, coronary, disease, (E. P. Boas and N. F. Boas), <sup>br</sup>78
- coronary disease, evaluation of anginal pain in various stages of, (H. L. Jaffe, et al.), <sup>ab</sup>203
- left coronary, from pulmonary artery, (P. E. Kaunitz), <sup>ab</sup>70
- pulmonary, isolated interventricular septal defect with dilation of the, an entity, \*317
- pulmonary, origin of left coronary artery from, (P. E. Kaunitz), <sup>ab</sup>70
- Arthritis, conjunctivitis, and urethritis (so called Reiter's syndrome) in a four year old boy, (A. Florman and H. Goldstein), <sup>ab</sup>346
- Aseptic necrosis in Gaucher's disease, (A. M. Arkin and A. J. Schein), <sup>ab</sup>267
- Association of psychosomatic disorders and their relation to personality types in the same individuals, (E. Moschcowitz and M. B. Rondin), <sup>ab</sup>204
- Atresia, tricuspid, with transposition of the great vessels: successfully treated by surgery, \*328
- tricuspid valve with transposition of the great vessels, (A. Robinson and J. E. Howard), <sup>ab</sup>77
- Auriculoventricular heart block, mechanism of irregular sinus rhythm in, (I. Roth and B. Kirsch), <sup>ab</sup>347

- B**ACTERIOLOGICAL aspects of the pathogenesis of tuberculosis, \*229
- Becker, M. C., Inspiratory increase of the pulse amplitude, its relation to pulsus paradoxus, \*132
- Behrman, Howard T., Another occupational mark, \*44
- Benign and malignant bone tumors, case of coexistent, \*187
- Bergman, P. S., Hemangioma of the pons. Case report and review of the literature, \*119
- Beriberi heart disease, course of, in American prisoners-of-war in Japan, (R. J. Allerman and G. H. Stollerman), <sup>ab</sup>145
- Berne, R. M., Role of antibodies in insulin resistance. Report of a case, \*102
- Biological method for determination of curare and erythroidine alkaloids, (E. P. Pick and G. V. Richards), <sup>ab</sup>74
- Bladder, urinary, amyloid disease of, \*254
- Bleeding, vesical, origin in the menopause confused with uterine and rectal bleeding, (I. C. Rubin), <sup>ab</sup>74
- Blood, coagulation of, defective thermal, \*1  
     fluorophotometric method for the estimation of salicylate in, (A. Saltzman), <sup>ab</sup>268  
     high penicillin levels, achieved with caronamide in penetrating the blood-brain barrier, (H. D. Janowitz, et al.), <sup>ab</sup>346  
     human, hyaluronidase inhibitor of, serum in health and disease, \*207  
     pressure, effects of dibenamine on, in normotensive and hypertensive subjects, (H. Haimovici and H. E. Medinets), <sup>ab</sup>69  
     viscosity, intravascular digital, effect of anemia and polycythemia on, (M. Mendlowitz), <sup>ab</sup>349
- Blum, Lester, Exclusion of the dog heart by parabiosis, \*38
- Blumenthal, Sidney, Tricuspid atresia with transposition of the great vessels: successfully treated by surgery, \*328
- Borun, Raymond, see King, Frederick H., \*310  
     see Kroop, Irving G., \*317  
     see Lasser, Richard P., \*295
- Brahms, Sigmund, see Blumenthal, Sidney, \*328  
     see Grishman, Arthur, \*336  
     see King, Frederick H., \*310  
     see Kroop, Irving G., \*317  
     see Schwartz, Bernard M., \*323  
     see Sussman, Marcy L., \*272
- C**ANCER, defective thermal coagulation of blood in, \*1  
     lung. Interval and late results of operation in relation to topography and gross pathology, (H. Neuhof and A. H. Aufses), <sup>ab</sup>205  
     roentgen therapy of, \*46
- Carcinoid of the duodenum, \*260
- Carcinoma of the gall bladder, (J. H. Garlock and F. P. Sainburg), <sup>ab</sup>68
- Cardiovascular disease, and congenital heart disease, research on, at The Mount Sinai Hospital, \*269
- Caronamide, role of high blood penicillin levels achieved with, in penetrating the blood-brain barrier, (H. D. Janowitz, et al.), <sup>ab</sup>346
- Case of coexistent benign and malignant bone tumors, \*187
- Catheterization, cardiac, and angiocardiology, technique of, as employed at The Mount Sinai Hospital, \*272  
     cardiac, electrocardiographic abnormalities induced by, \*295
- Cerebellum, granuloblastoma, a primary neuroectodermal tumor of the, (J. Epstein and A. Sacccone), <sup>ab</sup>267
- Cerebral arteriography, (S. W. Gross), <sup>ab</sup>75  
     arteriography in subarachnoid hemorrhage, (I. S. Wechsler and S. W. Gross), <sup>ab</sup>72
- Cesarean section, sulfadiazine and penicillin prophylaxis in, (R. G. Douglas and R. Landesman), <sup>ab</sup>349
- Chanley, J., see L. J. Soffer, \*98
- Chemotherapy, treatment of acute and subacute localized osteomyelitis with, (M. Oringer), <sup>ab</sup>350
- Chorda, tympani nerve graft. A preliminary report of a new technique used in surgical fenestration of the labyrinth, (S. Rosen), <sup>ab</sup>77
- Cholesterol metabolism in man, physiology of, \*79
- Cirrhosis, Laennec, its histogenesis with special reference to the role of angiogenesis, (E. Moschowitz), <sup>ab</sup>71
- Cold, whealing response to, (H. A. Abramson), <sup>ab</sup>72
- Comparative study of subtotal gastrectomy with and without vagotomy, (R. Colp, et al.), <sup>ab</sup>349
- Congenital heart disease, further experiences with microplethysmography in the study of, \*303  
     heart disease, research on, and cardiovascular disease, at The Mount Sinai Hospital, \*269
- Conjunctivitis, arthritis, and urethritis (so called Reiter's syndrome) in a four year old boy, (A. L. Florman and H. M. Goldstein), <sup>ab</sup>346
- Continuous fever of intestinal origin, (B. B. Crohn and H. Yarnis), <sup>ab</sup>147
- Coronary artery disease, (E. P. Boas and N. F. Boas) <sup>br</sup>78
- Creatine, endogenous, renal clearance of, in man, (J. Brod and J. Sirota), <sup>ab</sup>350
- Curare, action of, on erythrine alkaloids on morphinized mice, (E. P. Pick and G. V. Richards), <sup>ab</sup>76  
     biological method for determination of, (E. P. Pick and G. V. Richards) <sup>ab</sup>74  
     (intocorstin) in the acute state of anterior poliomyelitis, (D. Rosenberg and A. E. Fischer), <sup>ab</sup>146

**D**ACRYOCYSTITIS, silent, (F. Theodore),  
ab348

Defective thermal coagulation of blood serum in cancer and other diseases and its clinical interpretation, \*1

Depth dose curves for treatment grids in radiotherapy, \*49

Diabetes mellitus, mouth in, \*192

Diabetic, mid-leg amputations for gangrene in the, (S. Silbert), ab75

Dialysis of protein solutions for electrophoresis, (M. Reiner and R. Fenichel), ab347

Dibenamine, effect on blood pressure in normotensive and hypertensive subjects, (H. Haimovici and H. E. Medinets), ab69

Differential diagnosis of diaphragmatic hernia and coronary heart disease, (S. Dack, et al.), ab204

diagnosis of functional heart disturbances and organic heart disease, dihydroergocornine in, \*26

Digitoxin intoxication, (A. M. Master), ab204

Dihydroergornine in the differential diagnosis of functional heart disturbances and organic heart disease, \*26

Diseases of the heart, (C. K. Friedberg), br78

Drip therapy, intragastric, modern treatment of peptic ulcer with, (A. Cornell and A. Winkelstein), ab345

Dubos, R. J., Bacteriological aspects of the pathogenesis of tuberculosis, \*229

Ductus, arteriosus, patent, aortic septal defect, simulating, \*310

Duodenum, carcinoid of, \*260

gallstone obstruction of: case report, \*183

Dvorkin, J., see L. Scherlis, \*242

**E**DEMA, sodium, water and, \*159

Effect of dibenamine on blood pressure in normotensive and hypertensive subjects, (H. Haimovici and H. E. Medinets), ab69

of physically induced pyrexia on gastric acidity, (J. Bandes, et al.), ab75

Effect of anemia and polycythemia on digital intravascular blood viscosity, (M. Mendlowitz), ab349

Effects of single and double "two-step" exercise tests upon the electrocardiograms of 200 normal persons, \*242

Electric shock treatment in advanced pregnancy, (L. Simon), ab205

Electrocardiograms, effects of single and double "two-step" exercise tests upon the, of 200 normal persons, \*242

in infectious mononucleosis, (H. L. Jaffe, et al.), ab148

Electrocardiographic abnormalities induced by cardiac catheterization, \*205

changes phosphorus poisoning with recovery accompanied by, (R. A. Newburger and S. B. Beaser), ab205

changes, serial, in young adults with acute rheumatic fever, (N. Blackman and C. Hamilton), ab348

Electrogram, of the fish heart, (B. Kisch), ab70

Electrograms, exocardial and endocardial, and direct phonocardiograms in the calf, (B. Kisch, et al.), ab70

Electrophoresis, dialysis of protein solutions for, (M. Reiner and R. Fenichel), ab347

Endocarditis, subacute bacterial in mixed infection, (M. G. Olinger), ab73

subacute bacterial serological and biological characteristics and penicillin resistance of nonhemolytic streptococci isolated from, (S. S. Schneerson), ab74

Equilibration in vitro with alveolar air, pH of gastric mucous secretion after, (F. Hollander and F. W. Lauber), ab73

Esophagus, progress in the surgical treatment of carcinoma of the, and upper stomach, (H. Garlock), ab203

surgery of the, with special reference to; anesthesia in thoracic surgery, (S. Lyons), ab349

Evaluation of anginal pain in various stages of coronary artery disease. Particularly the premonitory phase of coronary occlusion and infarction without occlusion, (H. L. Jaffe, et al.), ab203

Evidence for an adrenergic component in the nervous mechanism of sweating in man, (H. Haimovici), ab147

Exclusion of the dog heart by parabiosis \*38

Exocardial and endocardial electrograms and direct phonocardiograms in the calf, (B. Kisch, et al.) ab70

Exophthalmic goiter, treatment of, in childhood, (A. Topper), ab344

Experimental observations on augmented unipolar extremity leads, (B. Kisch), ab70

**F**EITELBERG, SERGEI, see Megibow, Raymond S. \*303

Fenestration, surgical, of the labyrinth, a preliminary report on. Chorda tympani nerve graft, (S. Rosen), ab77

Fever, continuous, of intestinal origin, (B. B. Crohn and H. Yarnis), ab147

Fissure, anal chronic, surgical treatment of, (R. Turell), ab77

Fistula, anal, a necessary sequel to perianal abscess?, (E. Granet), ab69

Fluids, biologic, three way infusion valve for, (W. Bierman), ab345

Fluorophotometric method for the estimation of salicylate in blood, (A. Saltzman), ab268

Freud's scientific imagination, note on, (L. A. Spiegel), ab344

Further experiences with microplethysmography in the study of congenital heart disease, \*303



- G**ALL bladder, carcinoma of, (J. H. Garlock and F. P. Sainburg), <sup>ab</sup>69
- Gallstone obstruction of the duodenum: case report, \*183
- Gangrene of the extremities of venous origin, (H. Haimovici and G. Suffness), <sup>ab</sup>73
- mid-leg amputations for, in the diabetic, (S. Silbert), <sup>ab</sup>75
- Gargoylism, pathology of. Report of a case and review of the literature, (L. Strauss), <sup>ab</sup>269
- Gastrectomy, subtotal, with and without vagotomy, comparative study of, (R. Colp et al.), <sup>ab</sup>349
- Gaucher's disease, aseptic necrosis in, (A. M. Arkin and A. J. Schein), <sup>ab</sup>267
- Glass, George B. J., Defective thermal coagulation of blood serum in cancer and other diseases and its clinical interpretation, \*1
- Glick, D., Hyaluronidase inhibitor of human blood serum in health and disease, \*207
- Goiter, exophthalmic, treatment of, in childhood, (A. Topper), <sup>ab</sup>344
- Goldman, I. B., Restored viability of implanted preserved necrocartilage in rhinoplasty, \*142
- Gordon, Alvin S., see Grishman, Arthur, \*336
- see King, Frederick H., \*310
- see Kroop, Irving G. \*317
- see Lasser, Richard P. \*295
- see Schwartz, Bernard M., \*323
- see Sussman, Marcy L., \*272
- Gouty man, pool of miscible uric acid in normal and, studied with the aid of isotopic nitrogen, \*149
- Granuloblastoma, a primary neuroectodermal tumor of the cerebellum, (J. Epstein and A. Saccone), <sup>ab</sup>267
- Grids, depth dose curves for treatment in radiotherapy, \*49
- use of, in new approach to roentgen therapy of cancer, \*46
- Grishman, Arthur, Aberrant insertion of pulmonic veins, \*336
- see Sussman, Marcy L., \*272
- Group therapy with soldiers and veterans, (W. C. Hulse), <sup>ab</sup>346
- H**EART disease, coronary, differential diagnosis of diaphragmatic hernia and, (S. Dack et al.), <sup>ab</sup>204
- disease course of beriberi, in American prisoners-of-war in Japan, (R. J. Alberman and G. H. Stollerman), <sup>ab</sup>145
- disease, vitamin E in, (H. Levy and E. P. Boas), <sup>ab</sup>203, 204
- dog, exclusion of the, by parabiosis, \*38
- fish, electrogram of, (B. Kisch), <sup>ab</sup>70
- Hemangioma of the pons. Case report and review of the literature, \*119
- Hemorrhage, subarachnoid, arteriography in cerebral, (I. S. Wechsler and S. W. Gross), <sup>ab</sup>72
- Hernia, diaphragmatic, differential diagnosis of, and coronary heart disease, (S. Dack, et al.), <sup>ab</sup>204
- History, medical, of old age, life's later years studies in, \*53
- Hodgkin's disease localized to the anterior mediastinum: clinical, roentgen and surgical considerations, \*112
- Hyaline membrane of the iris, (J. Laval), <sup>ab</sup>76
- Hyaluronidase inhibitor of human blood serum in health and disease, \*207
- 2-Hydroxystilbamidine, urinary excretion of, \*21
- Hypertension, of the portal circulation, pathogenesis of splenomegaly in, "congestive splenomegaly", (E. Moschcowitz), <sup>ab</sup>145
- Hypertensive subjects, effects of dibenamine on blood pressure in, (H. Haimovici and H. E. Medinets), <sup>ab</sup>69
- I**LEITIS, regional, urological complications of, (I. Ginsburg and G. D. Oppenheimer), <sup>ab</sup>146
- Incontinence, anal, plastic repair for post-operative, (R. Turell, et al.), <sup>ab</sup>345
- Infection, mixed, in subacute bacterial endocarditis (M. G. Olinger), <sup>ab</sup>73
- respiratory acute, thrombophlebitis secondary to, \*176
- Infusion valve, three-way, for biologic fluids, (W. Bierman), <sup>ab</sup>345
- Inspiratory increase of the pulse amplitude, its relation to pulsus paradoxus, \*132
- Insulin resistance, role of antibodies in, \*102
- Intestinal origin, continuous fever of, (B. B. Crohn and H. Yarnis), <sup>ab</sup>147
- Intocostin, curare, in the acute state of anterior poliomyelitis, (D. Rosenberg and A. E. Fischer), <sup>ab</sup>146
- Intoxication, digitoxin, (A. M. Master), <sup>ab</sup>204
- Intracranial novocain anesthesia in frogs, (B. Kisch), <sup>ab</sup>267
- Iris, hyaline membrane of, (J. Laval), <sup>ab</sup>76
- Is anal fissure a necessary sequel to perianal abscess?, (E. Granet), <sup>ab</sup>69
- Isolated interventricular septal defect with dilatation of the pulmonary artery, an entity, \*317
- It takes training to be a good trustee, (J. Turner), <sup>ab</sup>147
- J**ACOBS, M. B., see L. J. Soffer, \*98
- Jarcho, Saul, Research on cardiovascular disease and congenital heart disease at The Mount Sinai Hospital, \*269
- Juvenile nasopharyngeal angiofibroma, (H. E. Ehrlich, et al.), <sup>ab</sup>72
- K**ATZ, J. F. Case of coexistent benign and malignant bone tumors, \*187
- Kent, D. S., see M. C. Becker, \*132
- Keratitis, deep, associated with atypical lichen planus, (J. Goldsmith), <sup>ab</sup>346
- Kernicterus. A review with a report of the findings in a study of seven cases, (P. Vogel and P. F. L. Becker), <sup>ab</sup>145

- King, Frederick H., Aortic septal defect simulating patent ductus arteriosus, \*310  
 see Grishman, Arthur, \*336  
 see Kroop, Irving G., \*317  
 see Lasser, Richard P., \*295  
 see Schwartz, Bernard M., \*323  
 see Sussman, Marey L., \*272
- Kuiskowky, E., Mouth in diabetes mellitus, \*192
- Kroop, Irving G., Isolated interventricular septal defect with dilatation of the pulmonary artery, an entity, \*317  
 see M. C. Becker, \*132
- L**ABYRINTH, a preliminary report of a new technic used in surgical fenestration of. Chorda tympani nerve graft, (S. Rosen), <sup>ab</sup>77
- Laennec cirrhosis; its histogenesis with special reference to the role of angiogenesis, (E. Moschowitz), <sup>ab</sup>71
- Laqueur, H. P., see L. J. Soffer, \*98
- Lasser, Richard P., Electrocardiographic abnormalities induced by cardiac catheterization, \*295  
 see King, Frederick H., \*310  
 see Kroop, Irving G., \*317
- Leads, augmented unipolar extremity, experimental observations on, (B. Kisch), <sup>ab</sup>70
- Leiter, H. E., Amyloid disease of the urinary bladder, \*254
- Lichen planus, atypical, deep keratitis with, (J. Goldsmith), <sup>ab</sup>346
- Lieben, F., see A. Saltzman, \*21
- Life's later years studies in the medical history of old age, \*53
- Light, whealing response to, with a note on the mechanism and the origin of the physical allergies, (H. A. Abramsen), <sup>ab</sup>72
- Loevinger, Robert, Depth dose curves for treatment grids in radiotherapy, \*49
- Lung, cancer of. Interval and late results of operation in relation to topography and gross pathology, (H. Neuhoof and A. H. Aufses), <sup>ab</sup>205
- M**ALIGNANT bone tumors, case of co-existent benign and, \*187
- Marek, F. M., see J. F. Katz, \*187
- Marks, Hirsch, New approach to the roentgen therapy of cancer with use of a grid, \*46
- Master, Arthur M., see Leon Pordy, \*26  
 see L. Scherlis, \*242
- Mechanism of adhesive plaster irritation, (S. M. Peck, et al.), <sup>ab</sup>146  
 of irregular sinus rhythm in auriculoventricular heart block, (I. Roth and B. Kirsch), <sup>ab</sup>347
- Mediastinum, anterior Hodgkin's disease, localized to, clinical, roentgen and surgical considerations, \*112
- Medical aspects of an alcoholic service in a general hospital, (M. Texon), <sup>ab</sup> 206
- Megibow, Raymond S., Further experiences with microplethysmography in the study of congenital heart disease, \*303  
 see Lester Blum, \*38
- Menopause, bleeding of vesical origin in, (I. C. Rubin), <sup>ab</sup>74
- Metabolism in man, cholesterol, physiology of, \*78
- Meyer, A., Obituary, \*265
- Microplethysmography, further experiences with, in the study of congenital heart disease, \*303
- Mid-leg amputation for gangrene in the diabetic, (S. Silbert), <sup>ab</sup>75
- Minowitz, Wilbert, see Robert Loevinger, \*49
- Mixed infection in subacute bacterial endocarditis; report of two cases, (M. G. Olinger), <sup>ab</sup>73
- Modern treatment of peptic ulcer with intragastric drip therapy, (A. Cornell and A. Winkelstein), <sup>ab</sup>345
- Mononucleosis, infectious, electrocardiogram in, (H. L. Jaffe, et al.), <sup>ab</sup>148
- Morphological backgrounds of "genuine lipoid nephrosis", (E. Moschowitz), <sup>ab</sup> 347
- Mount Sinai Hospital, research on cardiovascular disease and congenital heart disease at, \*269
- Mouth in diabetes mellitus, \*192
- Mucous, gastric secretion after equilibration in vitro with alveolar air, (F. Hollander and F. U. Lauber), <sup>ab</sup>73
- Murmur, apical systolic, (A. M. Master), <sup>ab</sup>76
- Myeloma, multiple, treatment of with stilbamidine. Clinical results and morphological changes, (I. Snapper), <sup>ab</sup>206
- N**ASOPHARYNGEAL angiofibroma, juvenile, (H. E. Ehrlich, et al.), <sup>ab</sup>72
- Necrocartilage, implanted preserved, restored viability of in rhinoplasty, \*142
- Necrosis, aseptic in Gaucher's disease, (A. M. Arkin and A. J. Schein), <sup>ab</sup>267
- Neoplasm, orbital, X-ray therapy for, (J. Laval), <sup>ab</sup>76
- Nephrosis, genuine lipoid, morphological backgrounds of, (E. Moschowitz), <sup>ab</sup>347
- Nerve, chorda tympani graft. A preliminary report of a new technic used in surgical fenestration of the labyrinth, (S. Rosen), <sup>ab</sup>77
- New approach to the roentgen therapy of cancer with the use of a grid, \*46
- Nicotine, postganglionic site of action, with special reference to the direct action on blood vessels, (H. Haimovici), <sup>ab</sup>267
- Nitrogen, isotopic, pool of miscible uric acid in normal and gouty man, studied with the aid of, \*149
- Note on Freud's scientific imagination, (L. A. Spiegel), <sup>ab</sup>344
- Novocaine, intracranial anesthesia in frogs, (B. Kisch), <sup>ab</sup>267

- OBITUARY**, Dr. Meyer, \*265  
Occupational mark, \*14  
Origin of left coronary artery from pulmonary artery, (P. E. Kaunitz), <sup>ab</sup>70  
Orthodontic therapy as limited by ontogenetic growth and the basal arches, (J. A. Salzmann), <sup>ab</sup>75  
Osteomyelitis, subacute and acute, treatment of, with chemotherapy, (M. Oringer), <sup>ab</sup>350
- PAIN**, anginal, evaluation of, in various stages of coronary artery disease, (H. L. Jaffe, et al.), <sup>ab</sup>203  
Palindromic rheumatism, (S. Davison), <sup>ab</sup>345  
Parabiosis, exclusion of the dog heart by, \*38  
Patch testing, new adhesive tape remover of particular value in, (A. W. Glick et al.), <sup>ab</sup>346  
Pathogenesis of splenomegaly in hypertension, of the portal circulation; "congestive splenomegaly", (E. Moschcowitz), <sup>ab</sup>145  
of tuberculosis, bacteriological aspects of the, \*229  
Pathology of gargoylism. Report of a case and review of the literature, (L. Strauss), <sup>ab</sup>344  
Penicillin administration *via* the vagina, (R. T. Walter, et al.), <sup>ab</sup>147  
levels, high blood, achieved with caronamide in penetrating the blood-brain barrier, (H. Janowitz, et al.), <sup>ab</sup>346  
sulfadiazine prophylaxis in cesarean section, (R. G. Douglas and R. Landesman), <sup>ab</sup>349  
serological and biological characteristics and resistance of nonhemolytic streptococci isolated from subacute bacterial endocarditis, (S. S. Schneiderson), <sup>ab</sup>71  
Person, P., see E. Knishkowsky, \*192  
Peters, J. P., Sodium, water and edema, \*159  
PH of gastric mucous secretion after equilibration in vitro with alveolar air, (F. Hollander and F. U. Lauber), <sup>ab</sup>73  
Phonocardiograms, direct and exocardial and endocardial electrograms in the calf, (B. Kisch, et al.), <sup>ab</sup>70  
Phosphorus poisoning with recovery accompanied by electrocardiographic changes, (R. A. Newburger and S. B. Beaser), <sup>ab</sup>205  
Photosensitization therapy of acne vulgaris, (A. Kurtin and R. Yontef), <sup>ab</sup>268  
Physiology of cholesterol metabolism in man, \*79  
Plaster, adhesive irritation, mechanism of, (S. M. Peck, et al.), <sup>ab</sup>146  
Plastic repair for postoperative anal incontinence, (R. Turell et al.), <sup>ab</sup>345  
Poisoning, phosphorus, with recovery accompanied by electrocardiographic changes, (R. A. Newburger and S. B. Beaser), <sup>ab</sup>205  
Poliomyelitis, anterior, curare (intocostarin) in the acute state of, (D. Rosenberg and A. E. Fischer), <sup>ab</sup>146  
Polivy, C., Carcinoid of the duodenum, \*260  
Pollack, H., see E. Knishkowsky, \*192  
Pous, hemangioma of, etc., \*119  
Polycythemia, effect of anemia and, on digital intravascular blood viscosity, (M. Mendlowitz), <sup>ab</sup>349  
Polyps, rectal, showing early malignant transformation, (H. Peskin), <sup>ab</sup>268  
Pool of miscible uric acid in normal and gouty man, studied with the aid of isotopic nitrogen, \*149  
Postganglionic site of action of nicotine with special reference to its direct action on blood vessels, (H. Haimovici), <sup>ab</sup>267  
Pordy, Leon, Dihydroergocornine in the differential diagnosis of functional heart disturbances and organic heart disease, \*26  
Portal circulation, pathogenesis of splenomegaly in hypertension of, "congestive splenomegaly", (E. Moschcowitz), <sup>ab</sup>145  
Pregnancy, advanced, electric shock treatment in, (L. Simon), <sup>ab</sup>205  
Progress in the surgical treatment of carcinoma of the esophagus and upper stomach, (J. H. Garlock), <sup>ab</sup>203  
Protein solutions, dialysis of, for electrophoresis, (M. Reiner and R. Fenichel), <sup>ab</sup>347  
Psychosomatic disorders, association of, and their relation to personality types in the same individuals, (E. Moschcowitz and M. B. Rondin), <sup>ab</sup>204  
Pulmonary stenosis, uncomplicated, \*323  
Pulse amplitude, inspiratory increase of, its relation to pulsus paradoxus, \*132  
Pyrexia, effect of, physically induced, on gastric acidity, (J. Bandes, et al.), <sup>ab</sup>75
- RADIOTHERAPY**, depth dose curves for treatment grids, in, \*49  
Rectal bleeding, confused with bleeding of vesical origin in menopause, (I. C. Rubin), <sup>ab</sup>74  
polyps showing early malignant transformation, (H. Peskin), <sup>ab</sup>268  
Renal clearance of endogenous creatine in man, (J. Brod and J. Sirota), <sup>ab</sup>350  
Reiter's syndrome, arthritis, conjunctivitis and urethritis, so called, in a four year old boy, (A. L. Florman and H. M. Goldstein), <sup>ab</sup>346  
Research on cardiovascular disease and congenital heart disease at The Mount Sinai Hospital, \*269  
Restored viability of implanted preserved necrocartilage in rhinoplasty, \*142  
Rheumatic fever, acute, serial electrocardiographic changes in young adults with, (N. Blackman and C. Hamilton), <sup>ab</sup>348  
Rheumatism, palindromic, (S. Davison), <sup>ab</sup>345  
Rhinoplasty, restored viability of implanted preserved necrocartilage in, \*142



- Roentgen considerations, clinical and surgical, Hodgkin's disease, localized to the anterior mediastinum, \*112  
therapy, of cancer, new approach, with the use of a grid, \*46  
Role of antibodies in insulin resistance. Report of a case, \*102
- SALICYLATE**, fluorophotometric method for the estimation of, in blood, (A. Saltzman), <sup>ab</sup>268
- Saltzman, A., Urinary, excretion of stilbamidine and 2-hydroxystilbamidine, \*21
- Salzman, E., Hodgkin's disease localized to the anterior mediastinum: clinical, roentgen and surgical considerations, \*112
- Sandberg, A. A., see L. Schleris, L., Effects of the single and double "two-step" exercise tests upon the electrocardiograms of 200 normal persons, \*242
- Schleris, L., Effects of the single and double "two-step" exercise tests upon the electrocardiograms of 200 normal persons, \*242
- Schwartz, Bernard M., see Sussman, Marcy L., \*272  
uncomplicated pulmonary stenosis, \*323
- Septal defect, interventricular, isolated, with dilatation of the pulmonary artery, an entity, \*317  
defect, aortic, simulating patent ductus arteriosus, \*310
- Serial electrocardiographic changes in young adults with acute rheumatic fever, (N. Blackman and C. Hamilton), <sup>ab</sup>348
- Serological and biological characteristics and penicillin resistance of nonhemolytic streptococci, isolated from subacute bacterial endocarditis, (S. S. Schneier-son), <sup>ab</sup>74
- Serum, blood, hyaluronidase inhibitor of human, in health and disease, \*207
- Shock treatment, electric, in advanced pregnancy, (L. Simon), <sup>ab</sup>205
- Sigmoid as a source of right sided symptoms, (A. S. Lyons), <sup>ab</sup>73
- Silent dacryocystitis, (F. Theodore), <sup>ab</sup>348
- Sinus rhythm, irregular, in auriculoventricular heart block, mechanism of, (I. Roth and B. Kisch), <sup>ab</sup>317
- Sodium, water and edema, \*159
- Soffer, L. J., Ultraviolet spectrophotometric method for the determination of,  $\Delta$  3,5 androstadienone-17 in the urine, \*98
- Snapper, L., see A. Saltzman, \*21
- Spectrophotometric, ultraviolet, method for the determination of  $\Delta$  3,5 androstadienone-17 in the urine, \*98
- Splenomegaly, pathogenesis of, in hypertension on the portal circulation; "congestive splenomegaly", (E. Moschowitz), <sup>ab</sup>145
- Steinberg, Morris F., see Sussman, Marcy L., \*272
- Stenosis, pulmonary, uncomplicated, \*323
- Stetten, DeWitt, Jr., Pool of miscible uric acid in normal and gouty man studied with the aid of isotopic nitrogen, \*149
- Stilbamidine, treatment of multiple myeloma with. Clinical results and morphologic changes, (I. Snapper), <sup>ab</sup>206  
urinary excretion of, \*21
- Stomach, upper, progress in the surgical treatment of the esophagus and, (J. H. Garlock), <sup>ab</sup>203
- Streptococci, nonhemolytic isolated from subacute bacterial endocarditis, serological and bacterial characteristics and penicillin resistance of, (S. S. Schneier-son), <sup>ab</sup>74
- Sulfadiazine and penicillin prophylaxis in cesarean section, (R. G. Douglas and R. Landesman), <sup>ab</sup>349
- Surgical treatment of carcinoma of the esophagus and upper stomach, progress in, (J. H. Garlock), <sup>ab</sup>203  
treatment of chronic anal fissure, (R. Turell), <sup>ab</sup>77
- Sussman, Marcy L., see Blumenthal, Sidney, \*328
- Technique of cardiac catheterization and angiocardiology as employed at The Mount Sinai Hospital, \*272
- Sweating, in man, evidence for an adrenergic component in the nervous mechanism of, (H. Haimovici), <sup>ab</sup>147
- Syndrome, Vogt-Koyanagi, (J. Laval), <sup>ab</sup>76
- Systolic, murmur apical, (A. M. Master), <sup>ab</sup>76
- TANG, Z. T.**, see A. Saltzman, \*21  
Technique of cardiac catheterization and angiocardiology as employed at The Mount Sinai Hospital, \*272
- Thannhauser, S. J., Physiology of cholesterol metabolism in man, \*79
- Thoracic surgery, anesthesia in; with special reference to surgery of the esophagus, (S. Lyons), <sup>ab</sup>349
- Three-way infusion valve for biologic fluids, (W. Bierman), <sup>ab</sup>345
- Thrombophlebitis secondary to acute respiratory infection, \*176
- Trattamento sul moderno dell'ipertiroidismo, (M. Volterra), <sup>ab</sup>348
- Treatment of acute and subacute localized osteomyelitis with chemotherapy, (M. Olinger), <sup>ab</sup>350  
of multiple myeloma with stilbamidine. Clinical results and morphologic changes, (I. Snapper), <sup>ab</sup>206  
of exophthalmic goiter in childhood. Report of a follow-up study in twelve cases, (A. Topper), <sup>ab</sup>344
- Tricuspid atresia with transposition of the great vessels: successfully treated by surgery, \*328
- Trustee, it takes training to be a good, (J. Turner), <sup>ab</sup>147
- Tuberculosis, bacteriological aspects of the pathogenesis, of, \*229



- Tumor, primary neuroectodermal, of the cerebellum, granuloblastoma, (J. Epstein and A. Saccone), <sup>ab</sup>267
- "Two-step", single and double, effects of, upon electrocardiograms of 200 normal persons, \*242
- U**LCER, peptic, modern treatment of, with intragastric drip therapy, (A. Cornell and A. Winkelstein), <sup>ab</sup>345
- Ultraviolet spectrophotometric method for the determination of  $\Delta 3,5$  androstadienone-17 in the urine, \*98
- Uncomplicated pulmonary stenosis, \*323
- Urethritis, arthritis, conjunctivitis (so called Reiter's syndrome) in a four year old boy, (A. L. Florman and H. M. Goldstein), <sup>ab</sup>346
- Uric acid, pool of miscible, in normal and gouty man, studied with the aid of isotopic nitrogen, \*149
- Urinary excretion of stilbamidine and 2-hydroxystilbamidine, \*21
- Urine, ultraviolet spectrophotometric method for the determination of  $\Delta 3,5$  androstadienone-17 in the, \*98
- Urological complications of regional ileitis, (L. Ginzburg and G. D. Oppenheimer), <sup>ab</sup>146
- Uterine bleeding, confused with bleeding of vesical origin in menopause, (I. C. Rubin), <sup>ab</sup>74
- V**AGINA, penicillin administration *via*, (R. I. Walter, et al.), <sup>ab</sup>147
- Vagotomy, comparative study of subtotal gastrectomy with and without, (R. Colp et al.), <sup>ab</sup>349
- Valve, three-way infusion, for biologic fluids, (W. Bierman), <sup>ab</sup>345
- tricuspid, atresia of, with transposition of the great vessels, (A. Robinson and J. E. Howard), <sup>ab</sup>77
- Veins, pulmonic, aberrant insertion of, \*336
- Vessels, blood, postganglionic site of action of nicotine with special reference to its direct action on, (H. Haimovici), <sup>ab</sup>267
- great, atresia of the tricuspid valve with transposition of, (A. Robinson and J. E. Howard), <sup>ab</sup>77
- Vitamin E in heart disease, (H. Levy and E. P. Boas), <sup>ab</sup>203, 204
- Vogt-Koyanagi syndrome, (J. Laval), <sup>ab</sup>76
- W**ALLERSTEIN, R. S., see R. M. Berne, \*102
- thrombophlebitis secondary to acute respiratory infection, \*176
- Wenner, J., see L. Scherlis, \*242
- Whealing response to light and cold with a note on the mechanism and the origin of the physical allergies, (H. A. Abramson), <sup>ab</sup>72
- X**-RAY therapy for orbital neoplasm, (J. Laval), <sup>ab</sup>76
- Z**EMAN, FREDERICK D., Life's later years studies in the medical history of old age, \*53











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